VOLUME 59 • APRIL 1958 • NUMBER 4

OPHTHALMOLOGY

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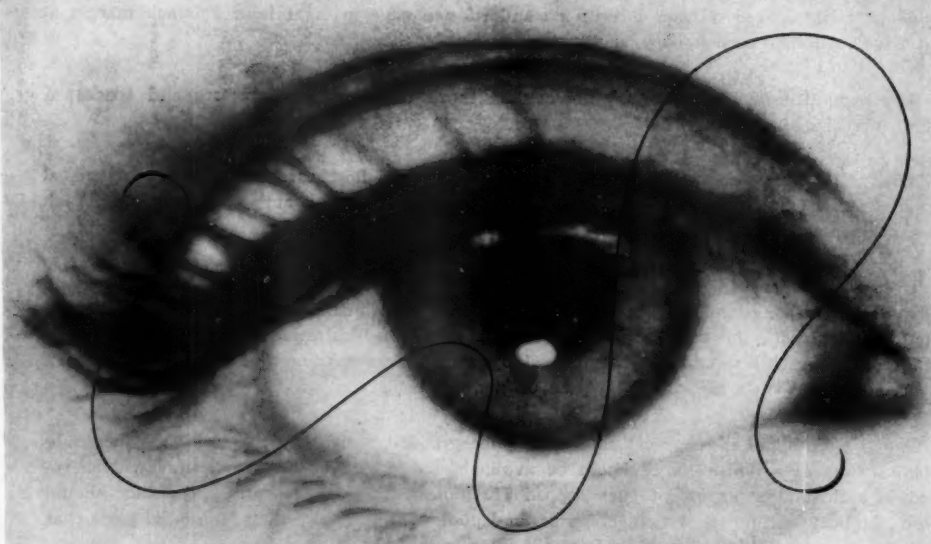

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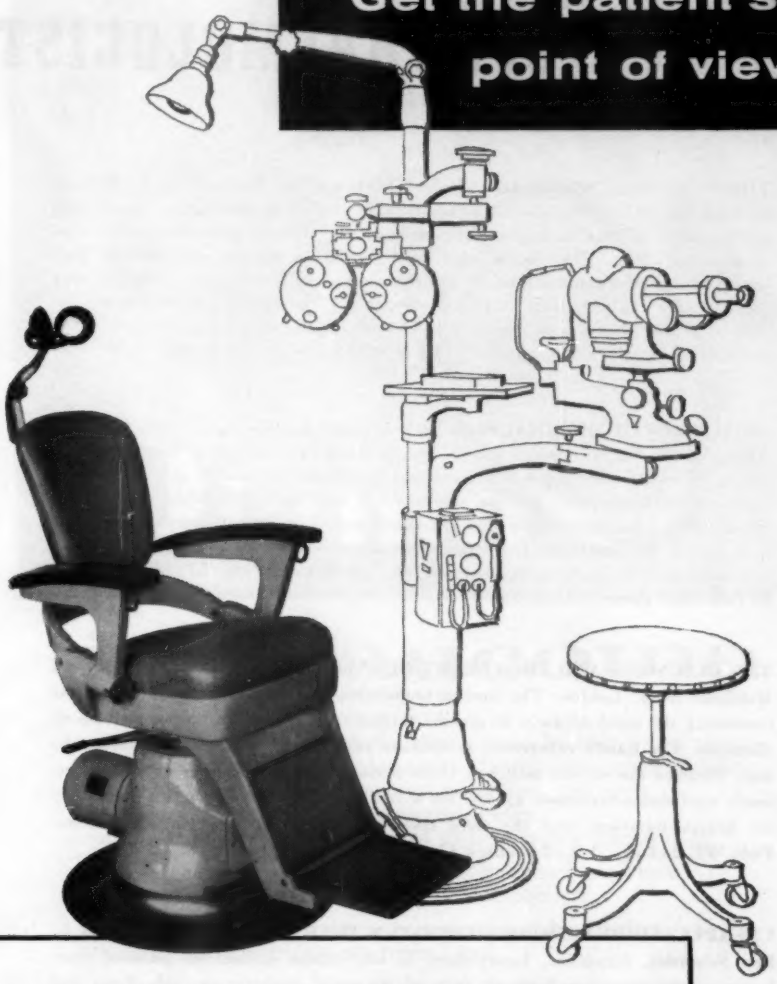

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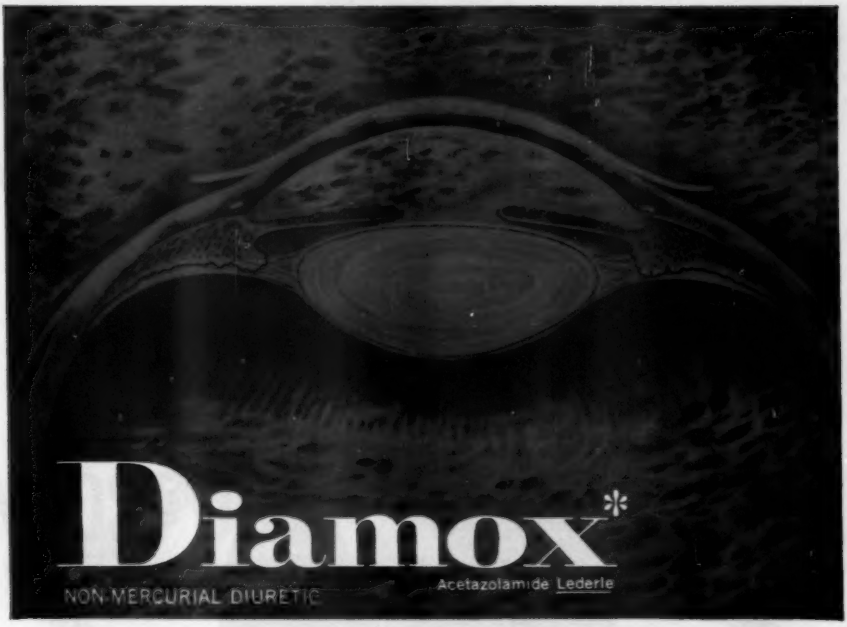

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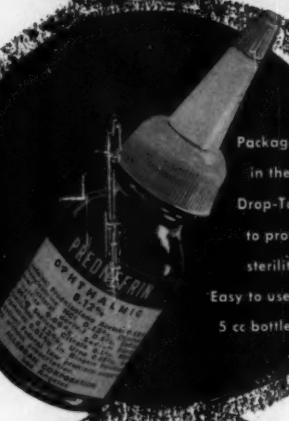

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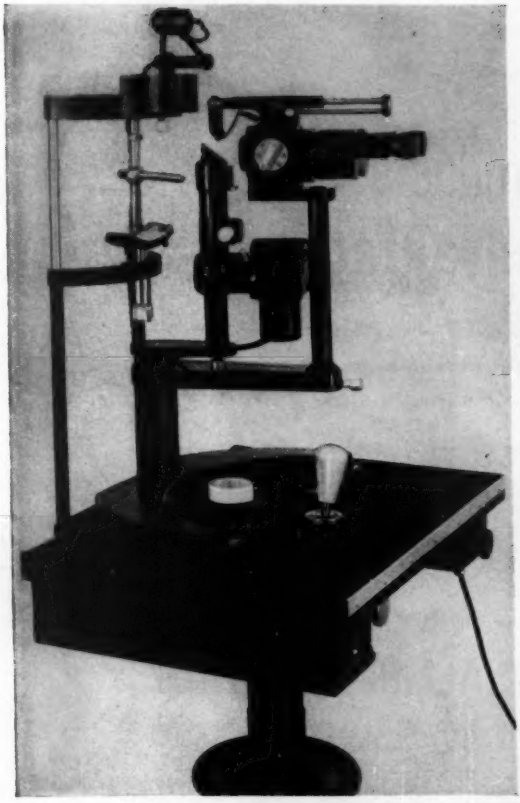

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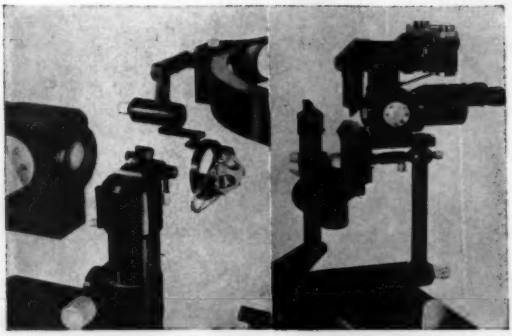

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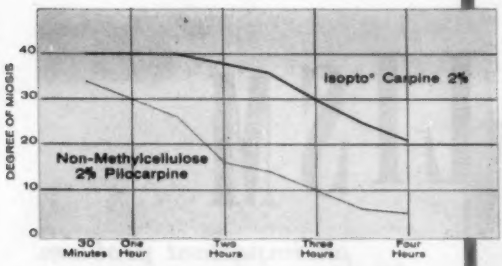

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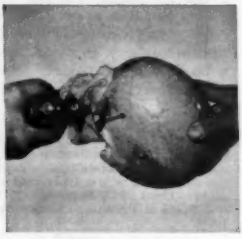

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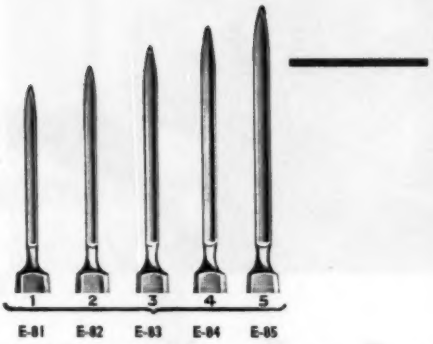

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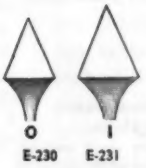

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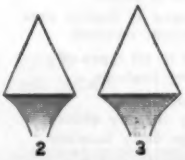

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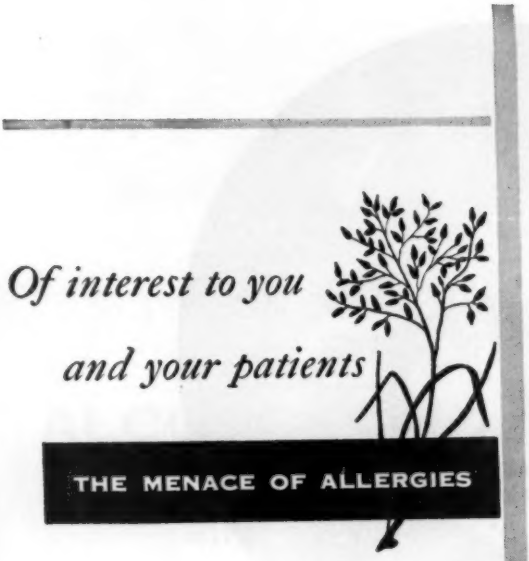

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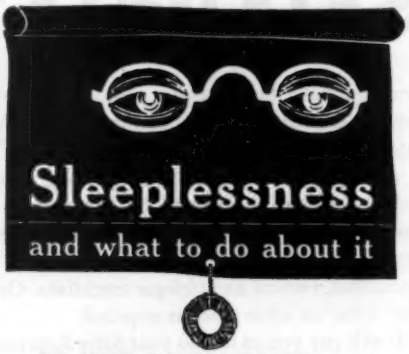

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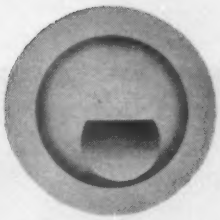

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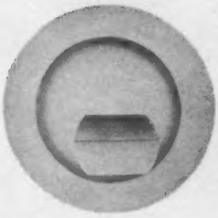

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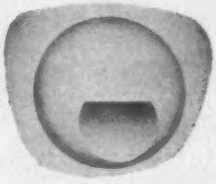

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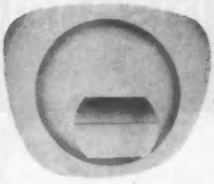

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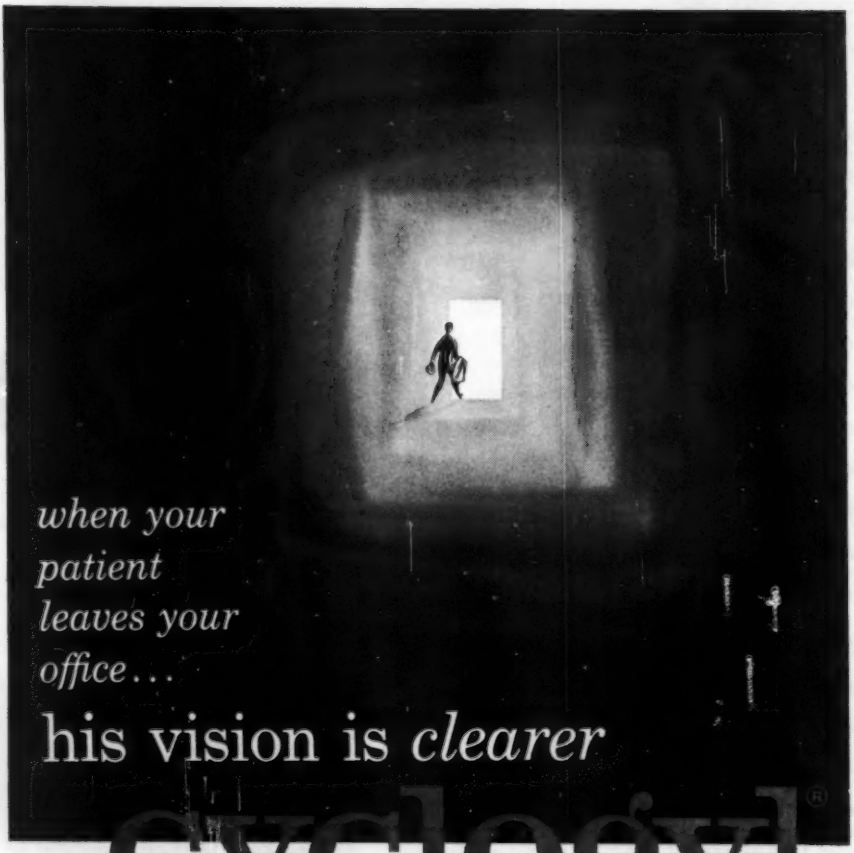

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Optic Neuropathy of Exophthalmic Goiter (Graves' Disease)

JOHN W. HENDERSON, M.D., Rochester, Minn.

Ophthalmologists who have frequent contact with persons afflicted with exophthalmic goiter (Graves' disease) are aware that many of these patients complain of some blurring of vision. In the majority of these situations the disturbance of vision is caused by a change in the refraction of the eye secondary to the factor of increased pressure in the orbits. Less frequently the blurring of vision is due to some change in the cornea secondary to its exposure or to glaucoma which develops in cases of exophthalmos accompanied by a marked increase in orbital pressure. In an occasional case papilledema is noted on ophthalmoscopic examination, and any defect of vision that subsequently develops is attributed to this disturbance at the optic papilla.

It is not well known that a disturbance of vision among these persons with endocrine exophthalmos may also develop as a result of an intrinsic disorder within the optic nerve which may not be accompanied by papilledema or any other visible manifestation of ocular dysfunction except loss of vision. In such situations the loss of vision cannot be explained except by performing studies of the visual fields. Throughout the voluminous literature on the subject of Graves' disease there are several reports of cases wherein a visual disturbance due to some lesion in the optic nerve was suspected but, because an examination of the visual field was not performed, the location of the disorder within the optic nerve was not proved.

To identify this particular type of disturbance within the optic nerve the term "retrobulbar neuritis" most frequently appears in the literature. In a recent review of the various types of disorders that may affect the optic nerve during the course of endocrine exophthalmos, Wagener [1] included references to reports on "retrobulbar neuritis" and "optic neuritis." In the majority of these references only one or two examples are reported, and because the observation periods are so short a long-term evaluation of the course and prognosis of the disease cannot be made.

Only in the reports of Igersheimer [2] (six cases) and of Hedges and Scheie [3] (six cases) are a sizable number of cases of this disease reported. Four of the six cases reported by Igersheimer (his Cases 2, 3, 4, and 6) can, by reason of the studies of the visual field and data reported, definitely be said to be examples of so-called retrobulbar neuritis.

Although a report of six cases would not be considered a significant contribution if judged by the usual standards of medical

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Section of Ophthalmology, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

reporting, it seems unusual for any one ophthalmologist to have the opportunity to observe even this many cases if the paucity of reported cases of this complication is considered in proportion to the number of persons with Graves' disease.

When the studies of Igersheimer and of Hedges and Scheie were published, I was collecting data on six cases that had been observed at the Mayo Clinic in the period 1951 to 1955, inclusive. In view of these publications I decided not to present my data as a separate study of the disease but instead to correlate them with those of Igersheimer and of Hedges and Scheie in order that a better over-all understanding of the behavior of this complication affecting the optic nerve might be obtained. By such a correlation conclusions can be drawn from a study of 16 cases by four observers (Igersheimer, four cases; Hedges and Scheie, six cases; six cases from Mayo Clinic). This will permit a more lucid evaluation of the disease than would be possible if single cases from multiple observers were correlated. A somewhat similar summary of the reports among the European literature was published by Danis and Bastenie.[4] These observers summarized the data collected from 12 cases that had been reported by eight different authors.

Summarized Reports of Cases

CASE 1.—A white man, 64 years of age, underwent initial examination at the clinic on July 17, 1951.

Thyroid Status.—Basal metabolic rate, +36%. Diagnosis: exophthalmic goiter.

Ocular Findings.—Visual acuity in right eye, 6/15; in left eye, 6/12. Results of ophthalmoscopic examination, negative. Hertel measurements: right, 23; left, 21; at base, 99. Eyelids retracted moderately; soft tissues of orbits were not edematous; globes were not chemotic. Examination of the visual fields showed bilateral central scotomas (Fig. 1).

Treatment and Course of Disease.—Subtotal thyroidectomy was performed on July 26. At final examination, on Aug. 3, 1951, the patient's vision was normal. The scotomas had disappeared, but the degree of exophthalmos and retraction of the eyelids remained unchanged.

CASE 2.—A white woman, 61 years of age, was examined at the clinic on May 6, 1953.

Thyroid Status.—She had been treated with radioactive iodine during September, 1952, for hyperthyroidism. In February, 1953, exophthalmos was noted. Four weeks prior to examination at the clinic visual blurring noted. Basal metabolic rate, +18%. Diagnosis: residual hyperthyroidism of minimal degree.

Ocular Findings.—Visual acuity in right eye, 6/30; in left eye, 6/12. Results of ophthalmoscopic examination, negative. Hertel measurements: right, 26; left, 27; at base, 116. There were marked edema of the eyelids, moderate congestion of the globes with minimal chemosis, and moderate

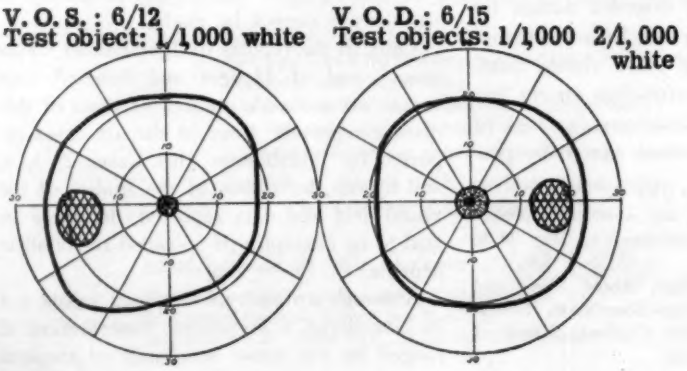

Fig. 1.—Bilateral central scotomas.

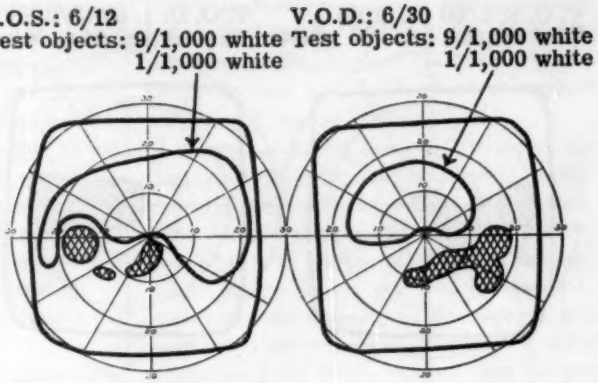

Fig. 2.—Relative central depression with arcuate scotomas.

ophthalmoplegia. The eyelids were not retracted. Visual fields showed central depression with arcuate scotomas below the fixation points (Fig. 2).

Treatment and Course of Disease.—Strong iodine (Lugol's) solution U. S. P. and desiccated thyroid were prescribed, and a course of x-ray treatment was given to the orbits. Examination elsewhere on Oct. 19, 1955, showed visual acuity in the right eye to be 6/6; in the left eye, 6/7.[5] Hertel measurements: right, 21½; left, 23; at base, 105.

CASE 3.—A 50-year-old white woman was first examined at the clinic on Sept. 20, 1951.

Thyroid Status.—History of partial thyroidectomy for "goiter" in February, 1950; in September, 1950, onset of exophthalmos; in March, 1951, blurring of vision first noted. An unknown amount of x-ray therapy had been administered to each orbit, and propylthiouracil had been prescribed. Basal metabolic rate, −12%. Considered euthyroid.

Ocular Findings.—Visual acuity in left eye, 6/60; in right eye, limited to ability to count fingers. Ophthalmoscopic examination gave negative results. Hertel measurements: right, 29; left, 28; at base, 112. Marked ophthalmoplegia and swelling of eyelids noted; moderate congestion and chemosis of globes. Visual fields showed central scotomas and peripheral contraction (Fig. 3).

Treatment and Course of Disease.—Bilateral orbital decompression was carried out on Oct. 3, 1951. At final examination, on Oct. 29, visual acuity had improved: right

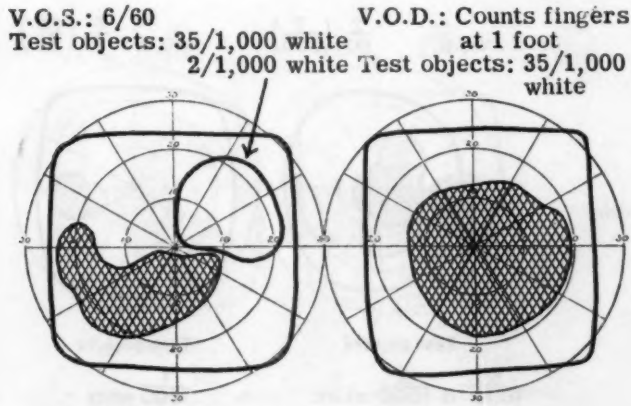

Fig. 3.—Relative central depression and arcuate scotoma, left eye. Central scotoma, right eye.

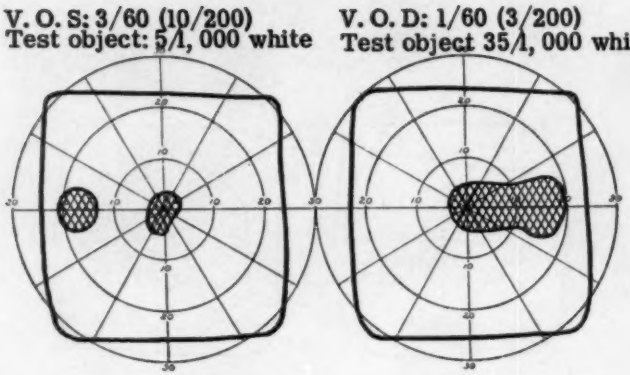

Fig. 4.—Bilateral central scotomas.

eye, 6/12; left eye, 6/15. Some recession of chemosis was noted; proptosis and ophthalmoplegia remained unchanged.

CASE 4.—A white woman, 46 years of age, underwent initial examination at the clinic on June 5, 1952.

Thyroid Status.—History of "thyroid operation" in December, 1950. In January, 1952, given "thyroid" because of dry skin, and in February, exophthalmos noted. Visual blurring noted three weeks prior to coming to clinic. Had had rheumatoid arthritis for 10 years. Basal metabolic rate, −16%. Diagnosis: mild myxedema.

Ocular Findings.—Visual acuity in each eye, 3/60. Results of ophthalmoscopic examination, negative. Hertel measurements: right, 24½; left, 25; at base, 105. Moderate ophthalmoplegia, swelling of the soft tissues, congestion of globes, marked retraction of eyelids, minimal chemosis. Examination of the visual fields disclosed central scotomas (Fig. 4).

Treatment and Course of Disease.—Desiccated thyroid and strong iodine solution U. S. P. were prescribed. At final examination, on Sept. 16, 1953, visual acuity had improved: right eye, 6/10; left eye, 6/6. A tiny central scotoma dense to 1 mm. white target at a distance of 2 meters was still present in the right visual field; the visual field of the left eye was normal. Slight abatement was noted in the ophthalmoplegia and exophthalmos.

CASE 5.—A white man, 63 years of age, came to the clinic for initial examination on Dec. 17, 1952.

Thyroid Status.—The patient had been treated for 11 years for low basal metabolic rate. Bilateral exophthalmos and decreased

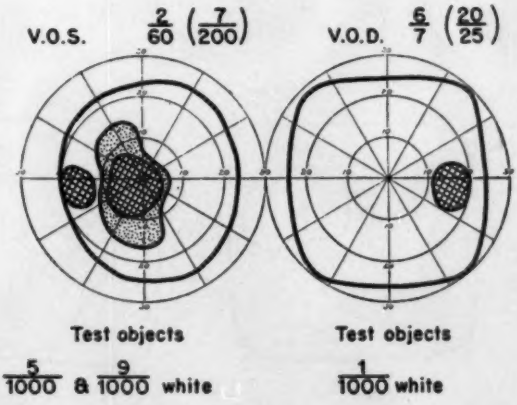

Fig. 5.—Central scotoma, left eye.

vision in the left eye were noted in the spring of 1952. In July his basal metabolic rate was high; administration of thyroid pills was discontinued, and that of propylthiouracil, commenced. Basal metabolic rate, −7%. He was considered euthyroid. Visual acuity in right eye, 6/7; in left eye, 2/60. Ophthalmoscopic examination gave negative results. Hertel measurements: right, 26; left, 28; at base, 105. Moderate congestion and chemosis of globes. Examination of visual fields showed a central scotoma in the left eye (Fig. 5).

Treatment and Course of Disease.—The patient was given desiccated thyroid and strong iodine solution U. S. P. Examination elsewhere in June, 1955, showed visual acuity corrected to 6/6 in the right eye and to 6/15 in the left eye.[6] Scotomas were not demonstrable with the 2/1000 white test object.

Case 6.—A 49-year-old white woman was examined at the clinic in April, 1954.

Thyroid Status.—History of swelling of the ankles, nervousness, and pain in the eyes of one year's duration. Basal metabolic rate, +44%. Diagnosis: hyperthyroidism. Normal vision, no exophthalmos. Radioactive iodine was given. In January, 1955, the patient seemed euthyroid clinically. In March, 1955, visual blurring was noted. In July, 1955, the basal metabolic rate was −12%. The patient was still considered euthyroid.

Ocular Findings.—Hertel measurements: right, 25; left, 26; at base, 105. Moderate ophthalmoplegia, marked chemosis. Visual acuity in each eye, 6/60. Bilateral central scotomas in visual fields (Fig. 6).

Treatment and Course of Disease.—In August, 1955, bilateral transfrontal orbital decompression was carried out. In October, 1955, visual acuity of the right eye was improved to 6/15 and the scotoma was smaller; visual acuity in left eye was decreased to ability to count fingers, and the scotoma was larger and denser. Final examination at the clinic, in June, 1956, showed visual acuity in the right eye, 6/6; in the left eye, 6/12. Scotoma in the right eye was not demonstrable with small test objects, but a tiny scotoma above the blind spot was still demonstrable in the left eye. The patient was euthyroid, and the degree of exophthalmos was less.

The findings in these 6 cases have been correlated with findings in 4 of the cases in Igersheimer's report and with those in the 6 cases of Hedges and Scheie—an over-all total of 16 cases (Table).

Results of Combined Study

Age and Sex Incidence.—A survey of the over-all series showed that all but 4 of the 16 patients were women. In 15 cases (in 1 case reported by Hedges and Scheie the patient's age was not stated) the ages ranged from 37 to 88 years. These two extremes

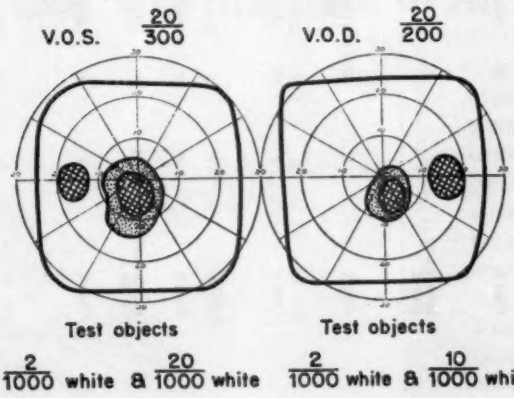

Fig. 6.—Bilateral central scotoma.

Summary of Data from Combined Study

Authors & Cases	Sex	Age, Yr.	Thyroid Status & Ocular Involvement	Vision of Affected Eye*	Visual Fields	Fundi	Treatment	Period of Observation	Comment
Hedges & Schein Case 1	F	Not known	Hyperthyroid; bilateral	R, 6/30 L, 6/12	Central scotomas	Negative	Not stated	9 to 12 mo.	Vision and visual fields returned to normal; recovery of vision occurred prior to control of thyrotoxic state
Case 2	F	37	Hyperthyroid; unilateral	6/150	Central scotoma	Negative	Not stated	9 to 12 mo.	Vision and visual field returned to normal; recovery occurred after control of hyperthyroidism
Case 3	M	68	Hyperthyroid (under control); unilateral	6/21	Defect in nerve-fiber bundle	Negative	Not stated	9 to 12 mo.	Vision and visual field returned to normal
Case 4	F	44	Hyperthyroid (in remission); bilateral	6/150	Defect in nerve-fiber bundle & central scotoma	Negative	Not stated	9 to 12 mo.	Vision and visual field returned to normal
Case 5	F	40	Euthyroid; unilateral	3/150	Central scotoma	Negative	Thyroid extract	9 to 12 mo.	Vision and visual field returned to normal
Case 6	M	56	Euthyroid (previous thyroidectomy); bilateral	R, 6/150 L, 6/150	Central scotomas	Papilledema		9 to 12 mo.	R, vision improved to 6/15; pallor of disk developed L, vision and visual field returned to normal
Igersheimer Case 2	F	65	Hyperthyroid (under control); bilateral	R, C.F. L, 6/15	R, central scotoma L, relative central depression	R. Pallor of optic disk L. Negative	Propylthiouracil	3 yr. 10 mo.	R, C. F. (no return of vision), pallor of optic disk L, 6/10 pallor of temporal portion of optic disk
Case 3	F	50	Hyperthyroid; bilateral	R, 6/60 L, 6/15	R, central scotoma L, paracentral depression	Negative	Not stated	1½ yr.	R, 6/6 field normal. L, 6/10 relative central scotoma
Case 4	F	67	Hyperthyroid; bilateral	R, 3/60 L, 6/15	R, central scotoma L, not stated	Negative	"Radioactive iodine, then with thyroid"; orbital depression on right side	1 yr. 9 mo.	R, vision improved to 6/12 L, vision improved to 6/10
Case 6	F	87	Euthyroid; bilateral	R, C.F. L, 1/60	Central scotomas	Negative	Thyroid & corticotropin	1 mo.	R, vision improved to 1/15 L, vision improved to 1/6
Henderson Case 1	M	64	Hyperthyroid; bilateral	R, 6/15 L, 6/12	Central scotomas	Negative	Subtotal thyroidectomy	1 yr. 11 mo.	Vision and visual fields returned to normal 6 days after thyroid operation
Case 2	F	61	Minimal hyperthyroidism; bilateral	R, 6/30 L, 6/12	Relative central depression with arcuate scotomas	Negative	Strong iodine solution, desiccated thyroid, x-ray to orbits	2 yr. 2 mo.	R, vision improved to 6/6 L, vision improved to 6/7

Case 3	F	50	Previous thyroidectomy & treatment with propylthiourecil; now euthyroid; bilateral	R, 6/60 L,	C.F.	Central scotomas	Negative	Bilateral orbital decompression	1 mo.	R, vision improved to 6/12 L, vision improved to 6/15
Case 4	F	46	Previous thyroidectomy; now has myxedema; bilateral	R, 3/60 L, 3/60		Central scotomas	Negative	Desiccated thyroid, strong iodine solution	1 yr. 3 mo.	R, vision improved to 6/10 L, vision improved to 6/6
Case 5	M	63	Previous treatment with propylthiourecil; now euthyroid; unilateral	L, 2/60		Central scotoma	Negative	Desiccated thyroid, strong iodine solution	2 yr. 7 mo.	L, vision improved to 6/15
Case 6	F	49	Previous hyperthyroidism treated with radioactive iodine; now euthyroid; bilateral	R, 6/60 L, 6/60		Central scotomas	Negative	Bilateral orbital decompression	2 yr. 2 mo.	R, vision improved to 6/6 L, vision improved to 6/12

* R, right; L, left; C. F., counts fingers.

of age were represented by female patients. The ages of the four men ranged from 56 to 69 years. Excluding the upper and lower age limits, the numbers of patients in each of the fifth, sixth, and seventh decades were nearly equal. The average age of the 15 patients was 56.5 years.

Thyroid Status.—When the thyroid status of the 16 patients was considered, there seemed to be a hodgepodge of findings. In six patients hyperthyroidism or thyrotoxicosis might have been a factor at the onset of the visual disturbance, and in another three cases, although hyperthyroidism had once been present, it seemed to be under control or was considered to be in remission at the time the patient was examined. Five of the patients were considered to be in a euthyroid state; one of them had previously undergone an operation on the thyroid. In one other patient operation had been performed on the thyroid prior to the visual difficulty, but this patient had mild myxedema when visual blurring occurred.

Ocular Findings.—Of the 16 patients surveyed 11 showed involvement of both eyes and 5 showed involvement of only one eye. The disorder, then, seemed to occur twice as frequently in both eyes as in one eye. On the basis of Hedges and Scheie's report alone (four unilateral and two bilateral cases), however, quite the opposite impression might be gained, whereas in my own six cases (five bilateral and one unilateral involvement) the disease was predominantly bilateral.

In trying to assess the severity of the hyperophthalmopathy on the basis of the amount of exophthalmos and the intensity of changes of the soft tissue and ophthalmoplegia in relation to the incidence of involvement of the eye, the data were studied from the standpoint of whether the orbital changes were mild, moderate, or severe. Although it was my prior impression that the ocular disorder occurred in severer instances of hyperophthalmopathy, no correlation could be found in this series of cases; as many

cases occurred in association with mild hyperophthalmopathy as with severe orbital disturbance.

Regarding vision itself, all degrees of visual impairment were noted. In most instances of bilateral involvement the visual loss was not the same in the two eyes. At no time did any of the patients show a visual loss beyond the ability to count fingers. Although the rapidity with which vision was lost was a factor difficult to assess accurately, it was my impression, based on the report by Hedges and Scheie as well as on my own cases, that the visual decrease occurred fairly rapidly, that is, over a period of two to six weeks, in most of the cases.

The defects in the visual fields showed a fairly consistent pattern, the loss of vision being due to a central or paracentral scotoma, to a defect of a nerve-fiber bundle, or to a combination of the two. The majority of patients showed the central scotoma type of defect, the scotoma possessing very sharp borders with a density varying from 1/1000 up to and including 35/1000 white test objects and varying in size from 5 degrees in diameter up to 30 degrees. As a rule, the periphery of the visual fields in these patients was unaffected.

The ophthalmoscopic examination among these patients consistently failed to show an explanation for the visual loss except in one of Igersheimer's patients. In his Case 2 temporal pallor of one optic disc was noted and doubtful temporal pallor of the other optic disc was recorded. In this particular case the pallor of the disc probably reflected the long duration of the visual loss. In one patient of Hedges and Scheie's series papilledema was present, but this was not believed to account for the type of defect that was present in the visual fields.

Course of Disease and Treatment.—A perusal of the 16 cases revealed that in 14 the course of the disease was characterized by a tendency of the visual loss to reach a climax and then to abate. In the two exceptions (one case reported by Igersheimer and one case reported by Hedges and Scheie in which there was bilateral involvement) the visual acuity in at least one eye of each patient remained poor, owing to the onset of optic atrophy. In the Igersheimer case pallor of the disc was noted at initial examination, and in the case of Hedges and Scheie papilledema was noted on the initial examination of the eye. On this basis it would seem that the presence of either pallor of the disc or papilledema at the time of the initial examination would prognosticate an unfavorable trend in so far as recovery of vision is concerned, but in all fairness it must be pointed out that although the other eye of the patient whose case was reported by Hedges and Scheie also exhibited papilledema a similar loss of vision was not present.

The degree of visual recovery varied considerably. On the basis of the report by Hedges and Scheie the evidence favored an excellent prognosis, because in five of their six patients vision returned to normal. However, among the remaining 10 cases only 1 patient recovered normal vision in both eyes and in 4 patients a final vision of 6/6 was noted in one of the involved eyes. In no instance was the patient left helpless by reason of poor vision in both eyes.

The patients of this combined study received a very representative cross section of nonsurgical as well as surgical treatment now in common usage for basic thyroid dysfunction. One or more of these patients received propylthiouracil, radioactive iodine, desiccated thyroid, strong iodine solution, corticotropin, x-ray irradiation to the orbits, subtotal thyroidectomy, decompression of the orbit, or combinations of several treatments during the course of observation. The effect of these various agents was such as to make it impossible to relate definitely either the onset of the visual failure or its improvement to the influence of any particular treatment. The course of the disease, in other words, seemed independent of the treatments attempted. In the survey of various cases collected among the literature as carried out by Danis and Bastenie,[4]

rather similar conclusions were reached as to the ineffectiveness of treatment in the course of the disorder.

Comment

In all case reports of this disorder wherein studies of visual fields were included the observers have placed the site of the disturbance in the optic nerve. In general, particularly in those cases in which papilledema was not present, the retrobulbar portion of the nerve has been suspected as harboring the pathologic change responsible for the scotomas. Indeed, the central scotomas and arcuate defects of the nerve-fiber bundle are very similar in configuration to the defects in the visual fields of patients with retrobulbar neuritis who do not have Graves' disease. Several observers, for these reasons, have designated this visual complication occurring during the course of Graves' disease as a retrobulbar neuritis, and the clinical behavior of these two disorders, characterized by a fairly rapid decrease in vision followed by some degree of improvement, is similar.

On the possibility that the factors responsible for the common type of retrobulbar neuritis not associated with Graves' disease are different from the factors contributing to the onset of the disorder of the optic nerve under discussion and to help differentiate the two disorders clinically, even though they have a common anatomic location, it is my suggestion that the term "optic neuropathy of Graves' disease" be used rather than the term "retrobulbar neuritis" until such time as the etiologic factors responsible for the disease are more clearly elucidated.

There is much speculation regarding the etiology and pathogenesis of this neuropathy. Terms such as "neurotoxic origin" or "toxic origin" have been used by several observers to explain the pathogenesis. In a situation such as that represented in Case 1 of my series, wherein the patient's recovery was exceedingly rapid on relief of the thyrotoxicosis, such a theory of neurotoxins would be difficult to refute. This theory, however, cannot explain all cases.

The other theory, the mechanical one, is a natural evolution from the clinical observation of increased volume of the retro-orbital tissues as well as increased orbital pressure that accompanies so many of the cases of so-called hyperophthalmopathy of Graves' disease. This theory, like the preceding one, does not apply to all cases, for there were many patients in this survey who did not exhibit a severe degree of hyperophthalmopathy. Likewise, I have seen many patients with hyperophthalmopathy of a degree much severer than that of any of the patients described in this survey who did not have any loss of vision due to a disturbance within the optic nerve. If mechanical factors, such as high orbital pressure, do affect the optic nerve, I would be inclined to hold these factors responsible for the papilledema that is seen in some cases rather than the neuropathy under discussion.

It is my feeling that the lesion also might be produced not by mechanical or toxic factors acting directly on the nerve fibers but instead by factors affecting the optic nerve indirectly through the medium of its vascular supply. An ischemic edema of the nerve (by this I mean a transient spasm of one of the nutrient vessels within the retrobulbar portion of the optic nerve followed by a transudation of fluid into the tissues with subsequent return of normal tone to the vessel and absorption of fluid) similar to that seen with a so-called central serous retinopathy might occur during the course of the hyperophthalmopathy. In disorders characterized by an ischemic edema there is often an initial severe degree of functional embarrassment of the part affected, with return of function as the edema subsides. If such a pathogenesis does exist, however, I have no idea as to the factor that triggers off the initial vascular spasm. In the few patients who did not show visual improvement, the initial spasm may have been of such duration as to impair the nutrition of the nerve fibers beyond the point of revers-

ibility, a pallor of the disc being the end-result.

Attention was directed earlier to the clinical fact that the majority of these patients do not show any papilledema or "papillitis." This does not preclude the possibility that papilledema may occur, as it does in a few instances, but when both central scotomas and papilledema are present in the same eye I consider this coincidental. The factors producing the papilledema are more likely to be the aforementioned mechanical forces, and the patients having hyperophthalmopathy who show only papilledema do not have loss of vision in the initial stages. If the papilledema in these particular cases is of short duration, vision will not be impaired, but if the papilledema is chronic or of long duration then secondary optic atrophy will occur. In this latter situation defects of the visual field usually will involve the periphery of the field (generalized contraction) first rather than produce the central scotomas characteristic of the neuropathy under discussion. In short, then, I consider the optic neuropathy of Graves' disease and papilledema to be manifestations of different mechanisms affecting the optic nerve during the course of the hyperophthalmopathy.

In the first several cases of this disorder that I observed I was anxious that the patients undergo orbital decompression lest vision become irreversibly lost. When some of the patients refused this well-meaning advice, I was greatly relieved, as was Igersheimer, to learn that vision improved without this surgical aid. As I have observed more patients having this condition and as I have benefited from the reports of other physicians who have encountered similar cases, I have come to the conclusion that loss of vision due to this disorder of the optic nerves need not be considered a positive indication for decompression. On the other hand, it is my feeling that for patients who have Graves' disease accompanied by papilledema, orbital decompression should be seriously considered as the treatment of choice.

Summary

Six cases of an infrequent and seldom-recognized disorder of the optic nerve occurring during the course of Graves' disease are described.

These 6 cases are correlated with 10 other cases recently reported from two different sources. On the basis of the study of this combined series, some conclusions are drawn as to the behavior of the disease.

The disorder is manifested by the demonstration of either central scotomas or defects of the nerve-fiber bundle on testing of visual fields. Its clinical course is similar to so-called retrobulbar neuritis. To help differentiate retrobulbar neuritis from the disorder under discussion the term "optic neuropathy of Graves' disease" is proposed.

Neither the clinical status of the thyroid gland at the onset of the disorder nor the usual treatments prescribed for the basic thyroid-pituitary dysfunction seem to have any influence on the course of the optic neuropathy. The disease has a good prognosis in that the majority of the patients have return of useful vision.

Some theories as to the possible pathogenesis of the optic neuropathy are discussed.

Mayo Clinic.

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The Effect of Cigarette Smoking on the Intraocular Circulation

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The practice of cigarette smoking is extremely widespread; nicotine is probably the most frequently used drug in the world, and yet the effect of smoking on the intraocular vascular system is very poorly understood. There are two broad reasons why our knowledge is so limited: First, the action of nicotine is diverse and complicated; second, the methods of studying the effects of drugs on the intraocular circulation are inaccurate, limited, difficult, or disturbing to the physiology. It is a widespread assumption that smoking causes a generalized constriction of intraocular blood vessels, but, as we will discuss, this is not necessarily true.

We will consider first some pharmacological effects of smoking and nicotine, then the actions of the drug nicotine on the vascular tree, and finally our own experimental findings concerning the effect of smoking and nicotine on the intraocular circulation.

A normal-sized commercial American cigarette weighs approximately 1 gm. and contains approximately 20 mg. of nicotine. The nicotine may be present either as the free base or as a salt. In the form of the free base it is more rapidly absorbed but more irritating than as a salt.[1] When the cigarette is smoked, approximately 35% of the nicotine is volatilized into the sidestream; that is, it goes off into the atmosphere. An additional 35% is destroyed at the burning tip, and approximately 6% condenses and is collected in the nonburning butt. Therefore, about 24% actually enters the smoker's respiratory system. If two-thirds of the cigarette is smoked, approximately 3.3 mg. of nicotine enters the respiratory system. If the smoker inhales, he absorbs 90% of the nicotine. We thus know that a person who smokes an ordinary cigarette and inhales receives a dose of 3 mg. of nicotine. As will be demonstrated subsequently, this is an ample amount to produce definite effects on the cardiovascular system of man or of animals. It is fortunate that nicotine is rapidly destroyed or eliminated, since a person who smokes two packages in a day receives 60 mg. of nicotine—a lethal dose.

It is important to establish the dose and action of nicotine, since it is this drug alone which causes the vascular effects of smoking. The other constituents of smoke—pyridine base, carbon monoxide, ash of cigarette paper, and others—produce no such effect.[2]

The pharmacologic action of nicotine is a complicated one. The main action consists of a primary transient stimulation and a secondary more persistent depression of all sympathetic and parasympathetic ganglia. But, in addition, nicotine stimulates the central nervous system, especially the respiratory, vasomotor, and emetic centers. There is also evidence that nicotine may act directly on the smooth muscle cells of the blood vessels to produce vasoconstriction.

It should be obvious from the above that the action of nicotine is not only complicated but unpredictable and that the actual effect on any given person will vary from marked vasoconstriction of peripheral ves-

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sels in one to vasodilation in another. For example, nicotine may increase the heart rate by excitation of the sympathetic or depression of the parasympathetic system or slow the heart rate by the reverse actions. In addition to this, the heart may be influenced by a direct effect on the medullary centers, plus compensatory reflex changes and a tendency for nicotine to produce a discharge of epinephrine.[3]

The practical importance of this is that patients will vary enormously in the vascular response to cigarette smoking.

Studies of the effect of cigarette smoking on a series of normal humans revealed that one out of five showed no response.[4] Of the majority (four out of five) who showed a response there was peripheral vasoconstriction, manifest by a drop in skin temperature, increase in blood pressure, and increase in pulse rate. This effect was generally more marked in women than in men, lasted from a few minutes to a half hour, and was more marked with rapid smoking than with slow smoking and with inhaling than with puffing.[5] A minority of persons reacted to cigarette smoking with peripheral vasodilation instead of constriction. It is interesting to note that this group had a marked aversion to smoking and regularly became nauseated and dizzy if they tried it.

The effect is only slightly reduced by the commercially available filters or denicotinized cigarettes. The nicotine in a cigarette must be reduced by more than 60% before the vascular effects of smoking fail to appear or are only slight.[6] The most effective filter is the lung,[7] and consequently the vascular effect is not eliminated by the much less effective commercially available filters. The desire for the vasoconstrictor effect of nicotine is so marked that the introduction of filters that reduce this effect has resulted in an increase in the sale of lower grades of tobacco containing more nicotine—thus nullifying the effect of filters.[8]

It is probable that peripheral vasoconstriction results in increased cerebral and intraocular blood volume, and the peripheral vasodilation is associated with a decrease in the latter. One can theorize that those patients with the marked peripheral vasoconstriction and central dilation may benefit from the latter as suggested by the statement of those who "need a cigarette in order to think clearly," whereas those persons who have been demonstrated to have peripheral vasodilation and an aversion to cigarettes associated with vertigo and nausea may experience the latter because of decreased cerebral blood flow.

In light of the variations in peripheral vascular response in a location in which the blood vessels are readily available to clinical and experimental study, it is not surprising that little is known regarding the response of the intraocular circulation to smoking.

Let us now consider the methods of studying the effect of smoking and nicotine on the intraocular blood vessels that are available to us. These may be grouped as follows.

I. Direct Observation of the Vessels of the Retina

These include direct observation with the ophthalmoscope, with or without a grid,[9] photography with a fundus camera,[10,11] and photography with a Leitz Ultropak microscope and a Koeppe contact lens. Within this group the only method of promise is to photograph the retinal vessels with a fundus camera and then to measure the retinal blood vessels while viewing the photograph through a low-powered microscope containing a micrometer in the ocular. This method was used by us and will be discussed later in this paper.

Direct observation with an ophthalmoscope is unsuccessful, since changes, if they occur, are in the order of 15% or less and are not appreciated. In addition to this difficulty, it is almost impossible to maintain fixation on a given segment of a vessel for a long period of time, and aberrations in different sections of the cornea may cause apparent variations in size more marked than the actual ones.

II. Direct Observation of the Blood Vessels of the Choroid

The scleral window technique of Leopold [12] involves the insertion of a plastic button under the sclera, removing the overlying sclera, and observation of the underlying choroidal blood vessels with a microscope. The technique obviously involves some trauma and only permits examination of the larger choroidal vessels. Leopold was unable to find any agent which would increase the diameter of these vessels, although several diminished the diameter.[13] We have not used this technique, and Leopold did not test smoking or nicotine by this method.

III. Secondary Physiologic Effects Resulting from Changes in Vascularity

Techniques dependent upon secondary physiologic effects resulting from changes in vascularity include electroretinography,[14-17] tests of flicker-fusion frequency,[18] angioscotometry, and changes in intraocular tension. All of these methods except the last can be influenced by changes in the retinal synaptic functions [19] as well as by vascular changes and therefore are not reliable.[20] Changes in intraocular tension are induced by so many factors that it is difficult to evaluate.

IV. Determination of Blood Volume Changes in Choroid and Retina by Use of Radioactive Phosphorus

Radioactive phosphorus has been used by us for several years in the study of various factors that influence the volume of blood in the choroid and retina.[21] Before reporting on our experimental results on the smoking of cigarettes and use of nicotine, we will present a brief review of the method itself.

In brief, this technique, adapted from Berson and Yalow,[22] is as follows: Radioactive phosphorus (P^{32}) is incubated with 10 cc. of blood withdrawn from an experimental animal (in this instance, a cat). This causes the P^{32} to enter into the red blood cells, where it is confined for a number of hours. The red cells are then centrifuged, washed three times, resuspended in saline, and reinjected into the animal. Thus, any P^{32} that did not enter the red cells is washed away. All of the radioactivity is contained in the red blood cells, which, in turn, are confined to the vascular tree. As the P^{32} is equally distributed throughout the vascular tree in a very short time, an increase in radioactivity means that a greater volume of blood is present under the counting tube. A decrease in radioactivity indicates the reverse.

The basis of this technique is demonstrated in the accompanying illustrations. If the P^{32} is not incubated into the red cells, it soon diffuses out of the blood vessel (Fig. 1). However, if the P^{32} is incubated into the red cells, all of the radioactivity is confined within the blood vessel (Fig. 2). If a Geiger-Müller tube is placed over the sclera, it detects the radioactivity in the blood vessels immediately below it. P^{32} emits only β-particles, which travel a maximum of 8 mm. through tissue. If the conjunctiva is

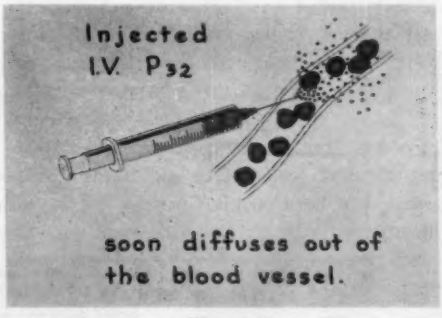

Figure 1

Figure 2

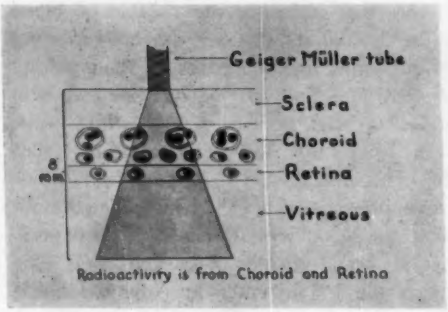

Figure 3

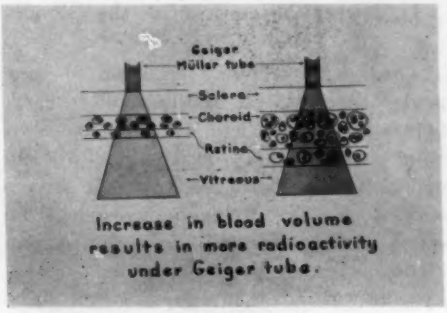

Figure 4

removed, a Geiger-Müller tube placed over the sclera, posterior to the ora serrata, could receive impulses only from the following tissues: the sclera, which contains a negligible volume of blood; the choroid, which contains most of the blood; the retina, with some blood, and the vitreous, which contains no blood (Fig. 3). As most of the blood is in the choroid, with some in the retina,[23] the radioactivity is derived from these structures. If the volume of blood in these structures is increased, more radioactivity will be detected by the Geiger-Müller tube (Fig. 4).

This new technique is the only one that permits the study of changes in the total blood volume of the choroid and retina. The associated experimental trauma is minimal. The technique has been used in a systematic study of factors that influence intraocular blood volume in cats.[24] During the course of these studies it was found that smoking, under certain conditions, increased the intraocular blood volume.

If an ordinary commercial cigarette was smoked very rapidly through the inhalation tube on the breathing machine, a significant and consistent rise in intraocular blood volume resulted (10 animals) (Fig. 5). It must be emphasized that this consistent change only occurred when the cigarette was smoked much more rapidly than usual. If the cigarette was smoked at an ordinary rate (in 7 to 10 minutes), no definite change in the blood volume resulted (Fig. 6). If a cigarette with part of the nicotine extracted (Sano brand was used) and more filtered out by use of a "Denicotea" filter was smoked at a moderate rate, no change occurred, but if it was smoked rapidly (two to four minutes) some increase in blood volume still took place.

If the usual commercial cigarette was impregnated with an additional 20 mg. of nicotine and then smoked at the usual rate, a variable increase in blood volume did occur in 13 of 15 animals.

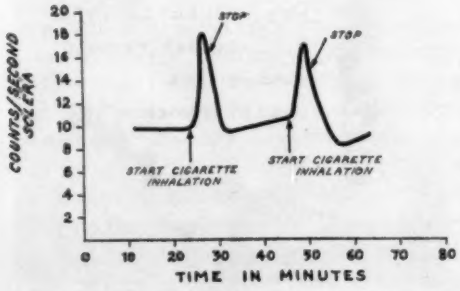

Fig. 5.—Effect of rapid smoking of cigarette.

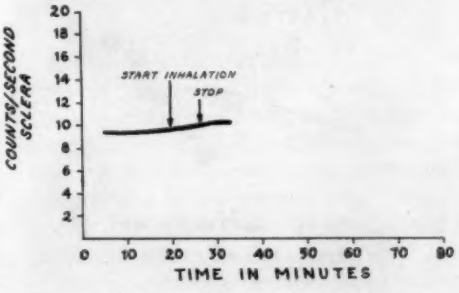

Fig. 6.—Effect of slow smoking of cigarette.

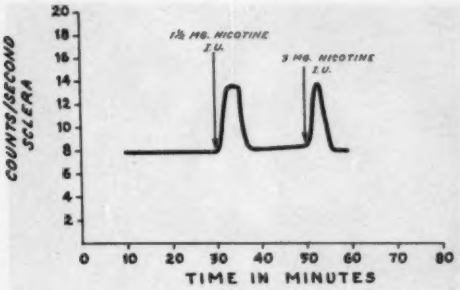

Fig. 7.—Effect of injection of nicotine solution.

That the increase in blood volume is due to nicotine, and not to some other factor in the smoking, is suggested by the above results and corroborated by the injection of a solution of nicotine intravenously. The effect of intravenous injection of nicotine is shown in Figure 7 (eight animals). The similarity to the effect of large doses of nicotine given by inhalation is obvious.

It is probable that the increase in blood volume within the eye is secondary to peripheral vasoconstriction and in this sense is a passive dilation.

There are objections to concluding that smoking in humans results in an increase in blood volume within the eye. These findings are on cats, not humans, and the smoking rate was more rapid and the dose per body weight was large. It has long been thought that nicotine constricts retinal vessels in humans. It must be remembered, however, that the effect of many drugs on the intraocular blood volume is frequently secondary to, and hence the opposite of, the effect on the peripheral vessels. The possible objection that the animals have never smoked before is probably not valid, since it has been demonstrated that acquired tolerance to the vasomotor effect of tobacco does not occur.[13]

Our technique used in cats was not considered applicable to humans, because the dose of P^{32} which could be used in humans was so low that statistically significant counts could not be obtained. Larger doses might result in legal action and therefore were not used.

Studies in Humans

In a search for a technique applicable to humans it was felt that examination of photographs of the retinal vessels under a dissecting microscope with a micrometer for accurate measurement might be rewarding. This technique had been used by Sieker and Hickam [15,25] in a study of the retinal vascular reactivity in response to inhalation of oxygen.

It was felt that this technique was definitely superior to the use of a graticule or micrometer in an ophthalmoscope as used by Cusick and Herrill many years ago.[27,28] We tried this but found it impossible to obtain dependable accurate measurements of the same area of the same vessel, and for this reason we decided on fundus photographs examined under the dissecting microscope.

These experiments were conducted in the following manner: A human subject had two control photographs taken of his fundus. A cigarette was smoked, and fundus photographs were taken when the cigarette was half smoked, when it was completely smoked, and 10 minutes after smoking. After a rest period another fundus photograph was made. The subject was then asked to breathe pure oxygen for five minutes, and an additional fundus photograph was made.

As oxygen inhalation had previously been demonstrated to constrict the retinal vessels, it was felt that the response to oxygen might serve as a control to demonstrate whether or not the technique worked and as a basis for comparison with the effect of smoking.

The photographs were enlarged, and then the enlarged print was examined under a dissecting microscope with ×10 magnification. A drawing of the photograph was made, and two points (A and B) on the arteries and two on the veins (C and D) were selected for comparative measurements. Each point was measured with a micrometer in the eyepiece of the microscope and recorded in arbitrary units. Any

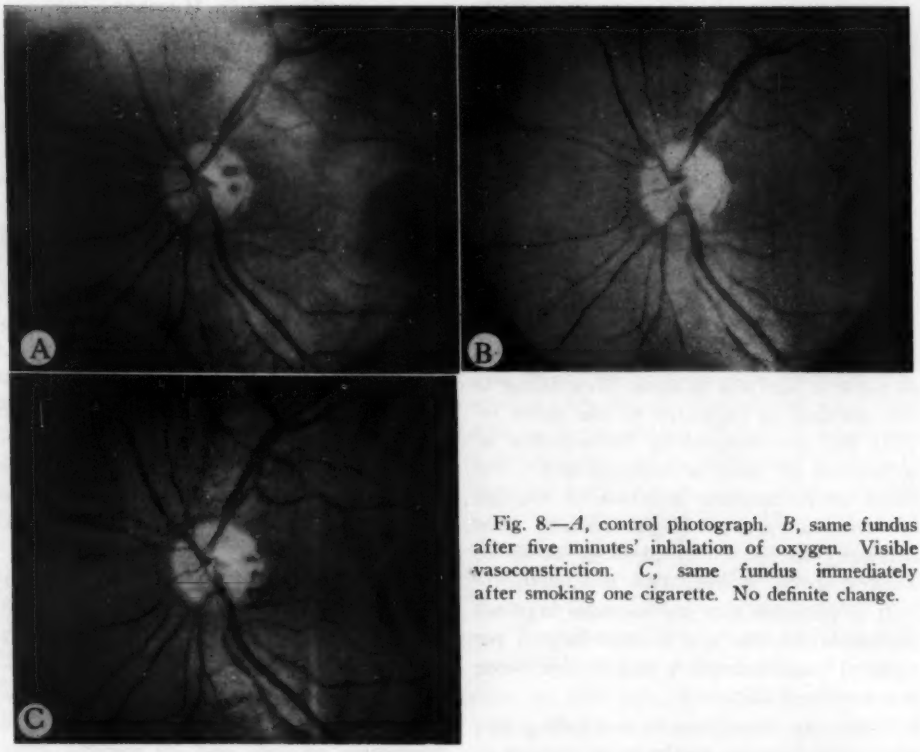

Fig. 8.—*A*, control photograph. *B*, same fundus after five minutes' inhalation of oxygen. Visible vasoconstriction. *C*, same fundus immediately after smoking one cigarette. No definite change.

change could be calculated in percentage of the original size (Fig. 8. *A*, *B*, and *C*).

Although more than 30 subjects were used, in only 18 were all of the pictures suitable; therefore our results are based on these 18 human subjects. All were apparently healthy, of ages from 19 to 40 years, and of varying smoking habits.

Each of the fundus photographs of the 18 subjects was carefully measured at two specific points on the arterial tree and two points on the venous side. Precisely these same points were measured on each control photograph and on the photographs taken after smoking one-half of a cigarette, after smoking the entire cigarette, 10 minutes after smoking the cigarette, and before and after inhaling oxygen for five minutes. Thus, there were four comparable points on each of the 18 subjects—a total of 72 points.

After one-half or one full cigarette was smoked 7 of the 72 points on the blood vessels showed vasoconstriction of an average of 0.8 units, and one showed dilation. Ten minutes after the cigarette was smoked only four of the points showed vasoconstriction and two showed dilation. After inhalation of oxygen for five minutes 26 of the 72 points (36%) showed vasoconstriction of an average of 1.0 units, and none showed dilation.

The oxygen inhalations were performed to demonstrate that the method was capable of detecting vasoconstriction of a moderate degree. That very few points responded after smoking shows that smoking rarely causes vasoconstriction in the human retinal vessels. In all instances the change was commoner in veins than in arteries.

Systemic reactions were checked by measuring blood pressure and peripheral skin temperature before and after smoking and before and after oxygen inhalation. Of the 18 subjects, 7 showed an increase of 10

Retinal Vascular Changes After Smoking *

	Vascular Points, No.			
	After 1 Full Cigarette		After Oxygen	
	Arteries	Veins	Arteries	Veins
Constriction	1	6	6	20
Dilation	1	0	0	0
No change	34	30	30	16
Av. change	0.8 units		1.0 units	

* There were 72 points measured in 18 subjects.

mm. of blood pressure or more after smoking and 13 showed an increase of 20 mm. or more. After oxygen inhalation 6 showed a decrease of 10 mm. or more and none showed an increase.

The skin temperature in five subjects increased 1 degree or more after smoking, and in eight it decreased 1 degree or more. In this group the skin temperature changes and blood pressure changes were not correlated.

The results of these experiments are shown in the Table.

Comment

The foregoing isotope experiments have indicated that smoking increases the blood volume of the choroid in experimental animals, provided the dose of nicotine is high. Our photographic experiments indicate that smoking constricts the retinal blood vessels in a few humans, changes them not at all in most, and may actually dilate them on rare occasions.

Let us consider the possible explanation of these apparently inconsistent results. We demonstrated at the outset of this paper that nicotine is a drug with multiple actions and varying effects. It is possible that the variations may be due to using cats for one type of experiment and humans for the other. It is more probable, however, that the retinal and choroidal vessels are fundamentally different. Oxygen caused no vasoconstriction of the choroidal vessels when tested on adult animals by the isotope technique. It is probable that retinal vessels respond more to direct stimulation, whereas the effect on the choroidal vasculature is likely to be secondary to alterations in blood supply elsewhere. Specifically, an agent capable of producing generalized vasoconstriction may cause the retinal and peripheral vessels to narrow, but the decrease in blood volume in the peripheral vessels may force more blood into the choroid. The choroidal vascular bed nourishes the outer portion of the retina, including the rod and cone layer, and consequently it is of fundamental importance, although it may respond differently than the retinal vessels.

Correlation of fundus photographs of retinal vessels in cats with choroidal changes in cats is to be done. Further elucidation of this problem may be made by the scleral window technique of Leopold, which we are now using.

Contrary to the popular opinion, it is possible that smoking may in some persons increase the intraocular blood supply rather than decrease it. It actually does not seem to produce vasoconstriction in a majority.

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Some Current Concepts of Headache, Especially Ocular

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Although considerable progress has been made in the investigation of the etiology and pathology of head pain and the mechanism of pain production, the diagnosis and treatment of many headaches are still perplexing problems, unsolved in some instances.[1] It has long been recognized that the primary symptom of a substantial number of patients consulting any ophthalmologist is headache; yet, it is also true that the exact cause of such pain is equally vague or unfamiliar to the physician. Certainly, it has been the experience of every eye physician to deal with many patients who feel very definitely that headache, which may be present in the areas adjacent to the orbit or in the eye itself, can be due to nothing except some ocular disturbance. This is far from the truth, and to discuss a few of the factors responsible for such head pain, especially as propounded by Wolff[2-4] and Roper,[1] and to propose a new concept of ocular headache is the purpose of this essay.

When a patient complains of headache, the physician is wholly dependent upon this statement, as it is an entirely subjective phenomenon. There is no sure way by which the doctor may determine whether the pain is organic or hysterical or whether it be even present at all; the intensity or frequency of the headache in no way determines the cause or significance of it, as headaches associated with the most serious conditions may be mild, while the severest and frequently recurring headaches may be compatible with general good health and long life.[1]

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Moreover, people who have head pain question the opthalmologist in regard to the possibility of brain tumor or glaucoma or cancer and are anxious to know whether they have been sufficiently investigated in these respects.

First and without question, the commonest type of head pain often localized around the eye is the so-called vascular, or tension, headache; a large number of cases of this type fall into the category of migraine, which everyone knows as a recurrent and periodic type, usually unilateral and associated with nausea and vomiting and, in about 10% to 15% of cases, preceded by visual disturbances. It frequently occurs in families and is usually improved by vasoconstrictor drugs; in some instances the temporal artery and its branches may be observed to be swollen and throbbing in the dilatation stage, and one also may see ophthalmoscopically, in a few cases, constriction and attenuation of the retinal arteries in the prodromal stages. It has now been rather conclusively shown by various investigators that during the painful phase of the migraine, or vascular, headache the pain is due to dilatation of pain-sensitive structures of the cranial blood-vessel system.[2] During the antecedent nonpainful phase there is often a vasoconstriction, which precedes the headache by 20 to 50 minutes, then follow minutes, hours, or days of head pain.

There are a great many varieties of such vascular headaches. If the headache happens to involve vascular structures in the upper frontal part of the head, the headache patient is apt to be seen by a physician interested in the eye. If it is accompanied by nasal manifestations, he is apt to be seen by someone who is primarily concerned with the air ways. When there is pain conspicuously involving part of the face, we again run into a great many varieties of names for such vascular

headaches. They include "Vidian neuralgia," "lower half headache" and "atypical facial neuralgia." If the headache involves the upper part of the head, then one really finds a great variety of names. Some of these are: Sunday headache, week end headache . . . menstrual headache . . . hot weather headache . . . constipation headache, indigestion headache, and so on.[3]

Thus, this type of headache can occur anywhere in the head; it can have practically any duration; it can be so mild that 10 grains (650 mg.) of acetylsalicylic acid may afford relief or of such severity that a large dose of morphine may have little effect —all have a similar mechanism in that distention of pain-sensitive cranial arteries occurs at one place or another in the head. What sets off this mechanism is still an unknown factor in the production of such head pain, but such pain may usually only be terminated after the use of vasoconstrictor agents which restore the vessels to their preheadache status.

Another classification of vascular headache is that associated with hypertension; about one-half of the persons with hypertension have headache, and it is not always present when the blood pressure is highest —in some cases the person's blood pressure becomes increasingly high as the headaches correspondingly become less frequent; there is, therefore, no close relationship between blood pressure level and headache. Yet it has been stated that sudden elevation of blood pressure will produce headache, but with sustained high blood pressure one need not have headache. To understand this, one must believe that the lability or contractile state of cranial arteries must be impaired when headache occurs and upon resumption of their ability to change caliber or to constrict one obtains relief of symptoms. Such headaches often come on in the morning and, as with migraine headache, increasing the intracranial pressure does not worsen them. This would lead one to believe that they may stem from pain-sensitive arteries outside the cranium.

The next in this series of considerations is headache resulting from skeletal muscle contraction of the head and neck. Some authors believe that this is the mechanism of eye headache, because of experimental work in which a person wearing lenses which produced double vision engaged in a period of close work, attempting all the while to merge the images. The investigator stated that during this time the extraocular muscles were undergoing sustained contractions as well as the muscles of the neck and shoulders. During this period, muscle potentials were recorded by an electomyograph, and during these contractions there developed not only pain in and around the eyes but also pain in the neck and shoulders.[4] Such symptoms seem to be corrobrated by other experimental workers, and this has been asserted to be the mechanism of a certain proportion of headaches due to ocular causes. Theoretically, correction of such ocular muscle abnormalities should relieve such headache, but there is not complete agreement upon this point.

It is well to remember that actually only a small percentage of headaches occur as a result of intracranial tumors, hemorrhages, or infections; by far the larger number occurs as a result of cranial vasomotor disturbances, skeletal muscle contraction about the head, or vasomotor disturbances in the nose.

Classification of the type of headache that is present in an individual case is based, then, on the site, source, and character of the pain; on the frequency and duration of attacks, and on the nature of associated manifestations, such as nausea and tinnitus. Head pain may originate in one of the following structures: (1) the tissues around the cranium, (2) cranial periosteum and endostium, and (3) certain intracranial structures, such as the great venous sinuses and their tributaries, parts of the dura at the brain base, and the dural and cerebral arteries; the trigeminal, glossopharyngeal, and vagus nerves and the first three cervical nerves are sensitive to pain. The cranium, the brain itself, most of the dura, the pia arachnoid, the choroid plexus, and the

ependymal lining of the ventricles are insensitive to pain; traction, displacement, distention, and inflammation of cranial vascular structures are chiefly responsible for headaches.[2]

The eyes and their adnexa have been explored for their sensitivity to pain in much the same way. Eckhardt, McLean, and Goodell[5] experimented on the pain-sensitive parts, both superficial and deep; secondly, on the headaches and eyeaches associated with refractive errors and extraocular muscle imbalances, and, finally, on photophobia.

They found that touch, pain, and cold are perceived through the conjunctiva, but there was no mechanism for recognizing heat up to 70 C.

The cornea perceives only pain and cold, while heat up to 70 C is not recognized as such; pinching, sticking, or cutting the extraocular muscles does not cause pain, but traction on them causes immediate deep orbital pain. Iris pain is likewise produced only by traction, referred to the eye itself and sometimes to the area of distribution of the opthalmic division of the fifth nerve. Increased intraocular pressure produces pain and sometimes nausea, and these investigators concluded that photophobia is a product of light stimulus and trigeminal irritation; if either of these sensory mechanisms is sufficiently depressed, photophobia disappears; vasodilation is not a necessary prerequisite. This is in contrast to Lebensohn and Bellows, who felt that local vasodilation was necessary for photophobia.

Lillie[6] (quoted by Roper[1]), noted that painful photophobia occurred in severe iridocyclitis but that in eyes with normal irides abnormal amounts of light never cause true pain but only sensations of discomfort or unpleasantness. He listed the eye conditions which usually produce localized pain over the area supplied by the first division of the fifth as acute dacryocystitis, foreign bodies and trauma of the conjunctiva and cornea, ulcerations of the conjunctiva and cornea, superficial and deep keratitis, iridocyclitis, acute congestive glaucoma, rupture of a choroidal vessel, periostitis and osteomyelitis of the orbit, orbital cellulitis, scleritis, suppurative endophthalmitis, secondary glaucoma, and exophthalmos. Also, certain conditions may produce a prodromal ocular pain without actually involving the eye, such as herpes zoster, actinic conjunctivitis, iritis, and sympathic ophthalmia. Trifacial neuralgia, petrositis, migraine, and thalamic syndromes usually produce severe pain without evidence of ocular involvement.[1]

Lillie seems to agree fully with Wolff's theory of the basic mechanism of headache, as he stated that "any lesion producing traction, displacement, distention or inflammation of any of structures supplied by the ophthalmic branch of the fifth nerve has the potentiality of producing eye pain, varying from slight uneasiness to extreme distress."

Our knowledge of these basic mechanisms has, therefore, increased, but it is still far from complete; the actual trigger mechanisms or basic cause of setting off these various courses of events is still unknown.

I shall consider, lastly, the relationship of eyestrain or asthenopia to headache, the commonest by far, which the opthalmologist encounters. Most patients believe that eyestrain is a well-defined entity having characteristic signs, symptoms, and causes and tending to produce permanent damage to the eyes. Every ophthalmologist has had innumerable patients who believe that the continued or excessive use of the eyes which is required in many occupations may lead to blindness or some form of visual loss. Actually, eyestrain is a very vague and ill-defined syndrome, and most physicians will agree that the commonest symptom associated with it is headache; the refractive errors, largely hypermetropia, astigmatism, accommodation, convergence anomalies, and muscle imbalances, are generally described as producing it. Eckhardt, McLean, and Goodell[5] found that headaches could be produced by artificially induced hyperopia,

astigmatism, and extraocular muscle imbalance but not usually by induced myopia.

Eyestrain headache occurs in many varieties and may be referred to any part of the area of distribution of the ophthalmic division of the fifth cranial nerve or upper cervical nerves; it is difficult to diagnose with certainty, conforms to no special type, and simulates many other types. The only logical procedure is to examine the eyes as a routine measure in all suspected cases.

The question may be asked as to what is the fundamental nature of eyestrain or asthenopia—what is it that is strained? This mechanism is not fully understood, but the production of head pain is presumably on the same basis as other referred pain of visceral origin.[1] I believe that eyestrain headache is a form of vascular headache. Experience with many patients has convinced me that it is not so much the actual refractive error or associated handicaps to vision that are responsible for the symptoms of many patients as it is the effort that is made to overcome the handicap. The conception of the eye as an optical instrument requiring adjustments and producing serious headache is commonly accepted, but in many persons the correction of the optical defect by no means entirely relieves the headache.

In 1941, Cogan[7] (quoted by Roper[1]) offered two very interesting speculations in regard to the production of symptoms of eyestrain; he noted (as other ophthalmologists have) that persons with small refractive errors, especially with small amounts of hyperopia and astigmatism, may have severe symptoms of headache, fatigue, irritability, and burning and smarting, whereas persons with refractive errors so large that presumably no voluntary effort was made to correct them have no eyestrain. Cogan points out that such patients often have eyestrain only after glasses have been prescribed, and, again, I would corroborate this in my own experience. He felt that the peripheral organ is not at fault and that the symptoms must be due to a central mechanisms that attempts to correct for the defect. He also presented the notion that the pains and discomforts arising from muscle imbalances are also of central origin. He noted the following observations in support of this thesis. If a patient maintains upward gaze for a substantial length of time, he will develop marked discomfort around the eyes terminating oftentimes in headache, but also a person who has a supranuclear lesion preventing him from looking up will have the same symptoms from the prolonged effort to look up. Here, there is no muscle contraction or accumulation of metabolic waste products from muscle contraction to explain the symptoms. Similarly, conditions of nystagmus, in which the eyes are constantly in motion over periods of years, produce no symptoms, whereas such movements performed voluntarily would lead to pronounced symptoms of fatigue.

These ideas are in agreement with the concept that it is not so much the error of refraction or muscle imbalance that is responsible for headache and other symptoms as it is the effort made to overcome the handicap; this may include such contributory factors as tension, stress, anxiety, or fatigue. Far from being simply a mechanical entity, eyestrain is a complex process extending into the psychologic realm and certainly not cured by objective examination alone.

In an attempt to analyze this combination of factors, a series of 50 patients whose major complaint was headache, persisting after errors of refraction had been corrected, was selected from my practice to determine the actual association of their headache with the use of the eyes for close work over a substantial number of consecutive working hours; 35 of these patients were either undergraduate or graduate students at metropolitan universities; 15 were adults engaged in constant desk work in business life. (This may seem like a relatively small number of cases, but it seems adequate to exemplify the point at issue.) Twenty-eight patients were female; twenty-two, male;

ages varied from 17 to 46, the average being 27. In every case organic causes of head pain were ruled out. All cases were hyperopic to the extent of at least 2 D., varying to one case who wore a correction of +800 sph; all also had an astigmatic correction of at least 0.75 D., ranging to a maximum of 3 D. In the case of the students, the study was carried on during their study periods for midyear and final examinations of 1955 and 1956, at which time is was customary for them to "cram for examinations" and to study an average of four to five hours daily and consecutively; in the cases of the 15 engaged in business life, they were all working under pressure and obtained permission from their employers to undergo this routine for a period of four weeks in 1955 and four weeks in 1956. The routine observed was as follows: First, all had careful refraction with correction of refractive errors and muscle imbalance; glasses were worn constantly. Second, during the period of study or intensive close work the person was requested to stop work at the end of 50 minutes of each hour. During the remaining 10 minutes he left his desk; in the case of the students, he completely relaxed by listening to music, lounging in a comfortable chair, or merely closing the eyes and resting. The business workers followed the above routine but were unable to enjoy music; following each period of 50 minutes of intensive work, 10 minutes of complete relaxation was observed. Excessive smoking was forbidden.

Every patient was also requested to have at least eight hours of sleep each night and to take a well-balanced diet, with some open air, exercise, and sunshine when possible.

After this period of observation of eight weeks was concluded, 33 of the 50 patients obtained almost complete relief from their headaches. In the remaining cases headache continued, but to a much less degree of intensity, and these patients were unable to follow the routine prescribed in as much detail; they, however, felt definite improvement and desired to continue the regimen.

It would appear, then, in this group of persons having very substantial refractive errors and engaged in long periods of intensive close work, that an important factor in the production of their headache might be attributed to the pain caused by tension, anxiety, apprehension, or stress rather than the mechanical factors of accommodation and fixation of the eyes.

It seems not improbable, therefore, that, in many cases, the mere correction of substantial errors of refraction and muscle imbalances is not sufficient to alleviate symptoms but that the unconscious and involuntary effort to see, apart from the mechanical correction of the optical defect, is a definite factor which produces as least a part of the symptoms resulting from sustained close work.

If the physician, in dealing with these cases, has the understanding, insight, and patience to delve into their commonplace problems and routine, in addition to correcting the mechanical visual defects, much can be accomplished in aiding and often curing such persons.

Summary

The commonest type of headache occurring in and around the eyes is the so-called vascular headache, due to arterial dilatation occurring in varying distribution through the cranium.

Head pain may result from innumerable ocular disorders, fundamentally arising from lesions in the eye producing vasodilation or traction or inflammation of pain-sensitive ocular structures.

Headache due to eyestrain or anisometropia is a vague and not completely explained condition, probably having a central psychologic basis; its pathogenesis has not been accurately determined but is may well fall into the category of vascular, or tension, headache.

It would appear that in many instances the head pain occurring in persons doing

sustained, close work and having adequate correction of anisometropia may be of vascular origin, also related to tension and stress.

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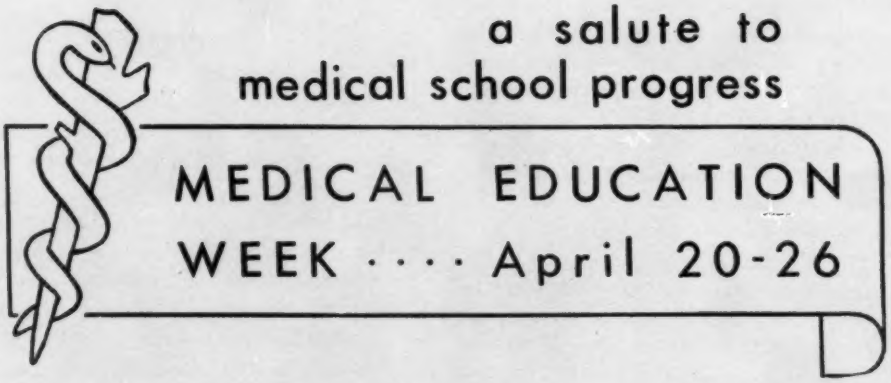

Corneal Changes from Quinone-Hydroquinone Exposure

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Staining of the cornea and conjunctiva, with precipitation of dark brown pigment granules within these tissues, is recognized as an industrial hazard for workers engaged in the manufacture of hydroquinone. In a previous report, submitted as a candidate's thesis to the American Ophthalmological Society, in 1946, one of us (B. A.) described certain characteristic lesions of the cornea and conjunctiva which had developed among a group of workers engaged in the manufacture of this chemical.[1] These studies indicated that the severity of involvement was proportional to the length of exposure and was conditioned by the cleanliness, and possibly to some extent by the age, of the individual worker. Although there are now a constant awareness of the possibility of seriously disabling exposure and strict supervision of plant and personnel, the development of ocular lesions among workers in this industry remains a problem. One of the preventative measures adopted as the result of the 1946 study has been the annual slit-lamp examination of exposed personnel. Any worker who shows evidence of appreciable exposure is now routinely transferred to another operative zone. Consequently, the characteristic heavy sepia staining of cornea and conjunctiva, with precipitation of dark brown granular material within these tissues, is no longer encountered. The conjunctival lesions have in fact regressed or disappeared in those persons removed from exposure hazards. For a numer of the men exposed prior to 1946, when the atmospheric concentration of hydroquinone was much higher than at present, the outcome has not been so favorable. For this group, the 1946 report, with the description of gross staining and pigment precipitation, in retrospect may be considered as having referred to the acute phase of the disease. These men have long been removed from any hazard of exposure to the chemical. It has become apparent, as the staining has cleared and the pigment has become absorbed, that the corneas of these men have undergone less spectacular but more insidious changes of a profound and irreversible nature. This paper is concerned with a description and discussion of these changes. They are probably not specific for hydroquinone exposure. Similar lesions might well result from prolonged exposure to any other chemical of such low toxicity. They are worthy of record because, through the opportunity afforded by the continuous observation of a large group of persons exposed over a long period to a minimal irritative insult, one may watch the gradual unfolding of changes in the cornea which finally lead to marked alterations in the corneal curvature, with resulting astigmatism.

In a screening test conducted in 1955 two hundred one persons, comprising almost all personnel who might have received significant exposure to hydroquinone (including some executive and clerical personnel), were examined by slit lamp. One hundred five of this group were found to exhibit evidence of exposure in varying degree. These were subdivided in accordance with severity of involvement into groups in accordance with criteria established in the 1946 report as follows: Group A, persons

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TABLE 1.—*Group C*

Case	Years Exposed	Stahli's Lines	Vertical Striae	Pterygium	Corrected Visual Acuity
9	21	+			O. D. 20/18, O. S. 20/17
3A	26	+			O. U. 20/29
106	11	+			O. U. 20/20
250	11	+			O. U. 20/17
136	8	+			O. U. 20/18
16	5	+	+		O. U. 20/18
196	3			+	O. D. 20/17, O. S. 20/15
96	12			+	O. D. 20/17, O. S. 20/15
86	13	+			O. D. 20/17, O. S. 20/15
62	9	+			O. D. 20/15, O. S. 20/17
57	22			+	O. D. 20/20, O. S. 20/18
60	6	+			O. U. 20/17
134	6	+	+		O. D. 20/22, O. S. 20/29
160	5			+	O. U. 20/17
117	12	+		+	O. U. 20/17
257				+	O. U. 20/20
10	17			+	O. D. 20/18, O. S. 20/29
198	6				O. D. 20/40, O. S. 20/25
48	21				O. U. 20/18
145	13				O. U. 20/18
37	21			+	O. D. 20/15, O. S. 20/18
203	7	+			O. D. 20/15, O. S. 20/17
193	13	+			O. U. 20/17
252	2	+			O. D. 20/15, O. S. 20/29

retired for extreme visual loss; Group B, persons transferred with severe visual loss; Group C, persons with moderate involvement; Group D, persons with insignificant staining.

In 1956 all available members of Groups A and B and certain members of Group C previously noted to have had potentially serious lesions were reexamined. We were concerned with the appearance of lesions which might represent various stages in the alteration of corneal curvature and, through the astigmatism thus induced, be responsible for the visual loss incurred by these patients.

The most prominent features of the moderately involved persons (Group C) were the prevalence of Hudson-Stähli lines and the occurrence of pterygia well above the percentage of the general population (Table 1). Hudson-Stähli lines were conspicuous in 14 of 24 persons who on previous examination had been found to have evidence of hydroquinone exposure. Eight of the twenty-four had also developed pterygia. Vertical striae, which were so conspicious a feature in Groups A and B, were present in only 2 of 24 persons in Group C. Other less constant findings were hyperesthesia; conspicuous, possibly enlarged, terminal nerve filaments, and loss of normal corneal luster.

None of the workers in Groups A and B (Table 2) have been exposed to hydroquinone within the last three years. All the conjunctival staining in these cases has disappeared. While it is of interest that pterygia have developed in only 2 instances in these 14 severely involved cases, in contrast to 8 such instances in the group of

TABLE 2.—*Groups A and B*

Case	Years Exposed *		Stahli's Lines	Vertical Striae	Pterygium	Refraction and Acuity
Group A						
1	10	8	+			O. D. 20/200, +2.50—5.00×45=20/70 O. S. 20/200, +2.50—6.00×100=20/70
3		14	+			O. D. 20/200, +2.50—4.50×75=20/50 O. S. 20/200, +2.00—3.00×90=20/60
7	16	11	+	+		O. D. 20/200, +1.50—2.25×45=20/200 O. S. 20/40, +1.75—2.50×135=20/29
8	13	11		+		O. D. 20/100, +2.50—5.00×75=20/40 O. S. 20/200, +2.50—5.50×110=20/100
10	11	9			+	O. D. 20/50 unavailable =20/40 O. S. 20/100 =20/50
44	15	3	+	+		O. D. 20/100, +4.00—5.00×30=20/200 O. S. 20/200, +3.50—2.50×150=20/67
51	21		+	+		Less than 20/200, O. S. and less than O. D.
Group B						
14	20		+	+		O. D. 20/50, +4.00—5.50×68=20/20 O. S. 20/50, +3.00—5.00×102=20/20
33	11	3	+			O. D. 20/33, +.50—1.25×60=20/25 O. S. 20/50, +.50—1.50×135=20/50
49	1	5				O. D. 20/29 unavailable =20/18 O. S. 20/25 =20/29
54	8	3				O. D. +1.12—.62×72 =20/20 O. S. +1.12—.37×100 =20/20
58	10	3	+			O. D. 20/33, +2.00—1.00×80=20/25 O. S. 20/50, +1.00—1.25×100=20/25
91	17	3	+	+		O. D. +1.50—1.50×90 =20/33 O. S. +3.50—5.00×100 =20/67
179	12	3	+	?	+	O. D. 20/200, +2.00—1.25×15=20/200 O. S. 20/33, +2.00—1.00×45=20/33

* The first figure in the second column refers to the number of years employed in hydroquinone. The second figure refers to interval in years since transfer from hydroquinone manufacture.

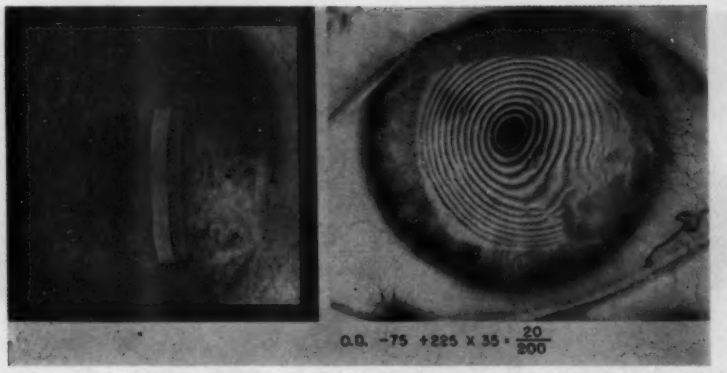


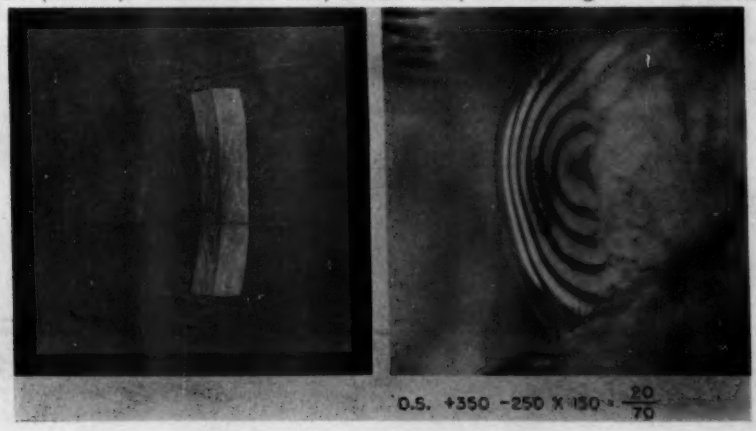
Fig. 1A (Case 7).—Hudson-Stähli lines, vertical striae, and flattening of corneal curvature.

24 who were moderately involved, the significance of this observation is unclear.

Ten of the fourteen men in Groups A and B have developed bilaterally conspicuous Hudson-Stähli lines. These lines were equally conspicious in 14 of the 24 moderately involved persons in Group C. They were the most constant and probably the earliest corneal changes in these cases. These lines are shown in slit-lamp drawings of the corneas of Cases 7 and 44 (Figs. 1A and 1B).

Vertical striae were observed in 2 of the 24 cases in Group C and in 7 of the 14 cases in the Groups A and B. These striae, which generally ran in a vertical direction, have also been illustrated in Figures 1A and 1B. They were widely interspersed and appeared as glass-like rods of somewhat sinuous and uneven pattern. One extremity seemed always to rest on Descemet's membrane. From this base, such a zone of optical discontinuity extended upward and forward within the stroma at an angle of some 30 degrees (Fig. 1A), always ending somewhat abruptly before reaching Bowman's membrane. The endothelium near the base appeared intact. There were no folds in Descemet's membrane, or at least no discontinuity in the smooth curve of the posterior corneal surface. The intraocular tension was normal. Raising the tension by pressure on the globe did not alter the appearance or the relative position of these lines. It was difficult to relate them with ruptures in Descemet's mem-

Fig. 1B (Case 44).—Hudson-Stähli lines, vertical striae, and flattening of corneal curvature.



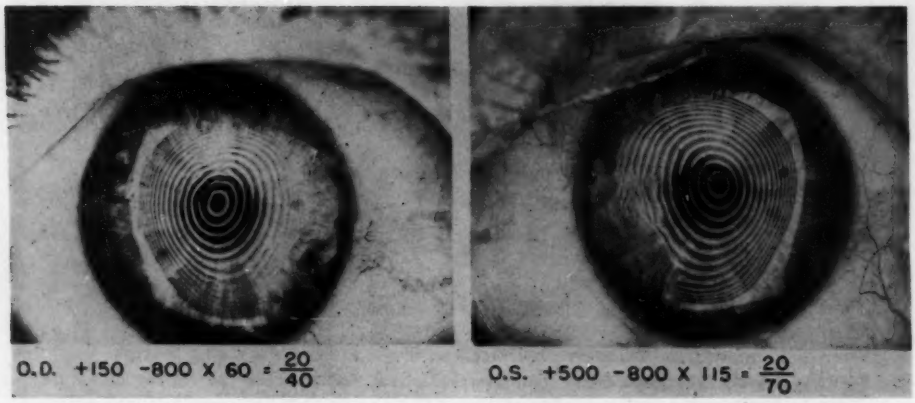


Fig. 2A (Case 8).—Extreme alteration (flattening) of corneal curvature without obvious localized scarring.

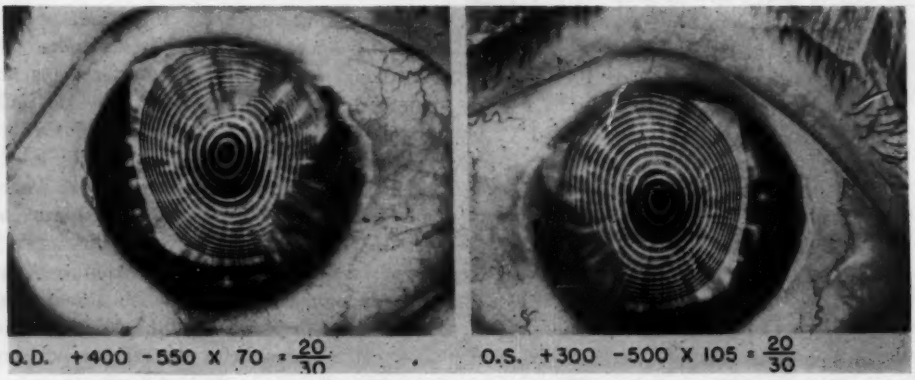
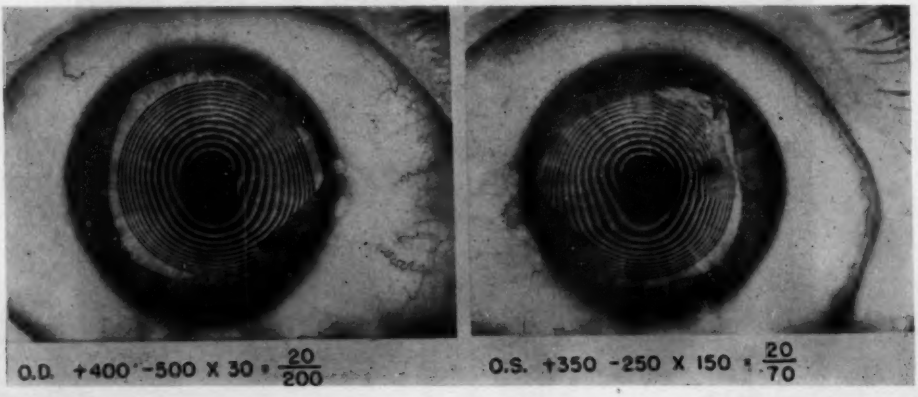


Fig. 2B (Case 14).—Extreme alteration (flattening) of corneal curvature without obvious localized scarring.

Fig. 2C (Case 44).—Extreme alteration (flattening) of corneal curvature without obvious localized scarring.



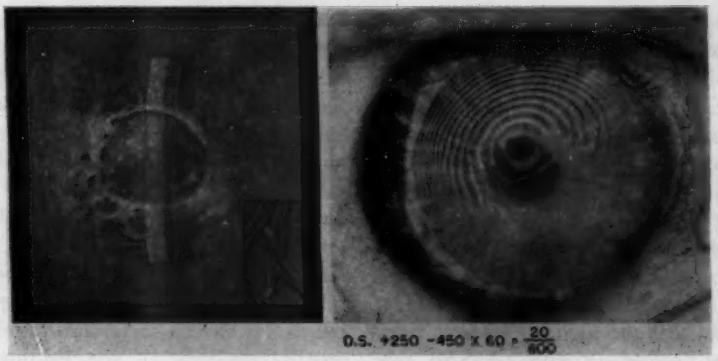


Fig. 3 (Case 51.)—Hudson-Stähli lines and vertical striae in an area of healed ulceration.

brane, since a zone of normal stroma usually intervened between Bowman's membrane and the most forward projection of the line. They were much coarser than the fine closely packed parallel vertical lines found etched into the cornea in keratoconus. The lines and the striae are much more conspicuous and sharply outlined than can be shown under the limitations of a black and white reproduction of the original drawings.

High astigmatic errors were not found in Group C. Astigmatism of more than 3 D. has developed in 8 of the 14 persons in Groups A and B. The photokeratographs of Cases 8, 14, and 44 (Figs. 2A, 2B, and 2C) show very graphically, particularly in the left eye, how this astigmatism has developed without obvious localized scarring.

These changes as demonstrated by slit lamp and photokeratographs of reflected Placido's rings result in a flattening of the central portions of the cornea. This flattening is shown in Cases 7 and 44 (Figs. 1A and 1B). Flattening even in the presence of healed ulceration is demonstrated in the drawing of the cornea of Case 51 (Fig. 3).

Comment

The development of pterygia in eyes exposed to long-standing low-grade irritation is generally recognized. It is therefore not surprising to find them in this incidence in this series. In fact their absence in the more severely involved group is more difficult to explain. Perhaps the appearance of the pterygia is an index to the degree of irritation. In this view, the lower incidence in the more severely involved group may indicate that the initial insult, although severer, was less prolonged.

What is the significance of the Hudson-Stähli line? This line was first described by Hudson in 1911, and it was described independently by Stähli in 1918. We picture such a line as a relatively well-defined somewhat sinuous streak consisting of greenish brown particulate granular material. This line lies horizontally and is most prominent just below the lower border of the undilated pupil. Its ends extend toward but do not meet the limbus. Usually it is located in a broader band of less distinct, more amorphous pigment or stain. Vogt thought this line to be similar to Fleischer's ring as seen in keratoconus.[2] This opinion may have some significance in reference to our own concept developed later in this paper. Hanssen,[3] after studying microscopic sections, concluded that the pigment, which he did not identify, was deposited between the epithelial cells and between these cells and Bowman's membrane as well as in this membrane and in the underlying stroma. Stocker has described two pigmented corneal lines, one developing and progressing in front and parallel with the broad axis of the pterygium and apparently associated with the inverse astigmatism which develops with the flattening of the cornea.[4] Stocker has described a second line of fine pigment

extending across the cornea, in which there was a melanotic pigmentation located in the corneal epithelial cells. Bowman's membrane was intact and free from pigment, as was the stroma.[5] Moncreiff[6] reported a yellowish-red streak of pigment lying beneath the epithelium anterior to Bowman's membrane horizontally across the cornea. In this case histologic section revealed the pigment to have a much wider distribution than was estimated from slit-lamp study. She thought that the pigment entered from the limbus and was concentrated in this line. Busacca[7] described two groups of corneal pigmentation, endogenous and exogenous. The endogenous, he thought, might be either melanin or hemosiderin. He did not fully explain the manner in which such pigmentation might reach or develop within the cornea. If melanin, the pigment could migrate from the limbus; if hemosiderin, it could come from the tears or the blood. Specifically, Stocker and Busacca proved by the Turnbull reaction for iron that the pigment in the Hudson-Stähli line, in the cases which they studied, was hemosiderin localized within the epithelial cells. In discussing exogenous pigmentation of the cornea, Busacca mentions without further comment the occurrence of interpalpebral pigmentation of the cornea in workers in chemical laboratories. Ferraris de Gaspare[8] succeeded in producing the characteristic lesions produced by hydroquinone in brown and albino rabbits under varying lighting conditions. After continuous exposure to finely powdered hydroquinone for several months a brown pigmentation was produced, localized first on the conjunctiva and later on the cornea. In animals exposed to light the pigmentation occurred earlier. This lead him to the conclusion that light probably influences the oxidative process which transforms hydroquinone into paraquinone within the tissues, thus causing the keratoconjunctival pigmentation.

These experiments lend support to our assumption, based on observation of corneal staining under working conditions, that the original staining as seen in 1946 was the result of a physiochemical reaction, an interaction with the corneal tissues of a chemical which is both water- and fat-soluble, in an alkaline medium (tears) aided by the mechanical action of the blinking lids. Unfortunately, we were unable, in the laboratory of industrial hygiene at Tennessee Eastman, to produce these lesions in albino rabbits by exposure to quinone vapor. Later efforts by Fassett in the laboratories of industrial medicine of the Eastman Kodak Company, with the use of black rabbits, likewise have been unsuccessful in producing such lesions. Nevertheless, it seems inconceivable that the massive staining of the ocular tissues was a purely mechanical reaction. Furthermore, the fact that we had previously demonstrated the presence of pigment within the basal cells[9] seems to support the biochemical theory of the origin of the pigment. Nishida[10] also demonstrated these "dense brownish black pigment deposits in the basal cells of the epithelium." It was his opinion that this pigment originated as a result of "impairment of cell enzyme activity due to deposits of benzochinone which is the oxidized substance of analine vapor." He considered the intracellular pigment to be melanin produced by abnormal tyrosine metabolism. Any epithelial cell is theoretically capable of producing melanin. The local environment established by the presence of oxidized hydroquinone (paraquinone) might well have stimulated the epithelial cells of the cornea to such an activity. The importance of all this relates to the probability that the pigment in Hudson-Stähli lines may under certain circumstances be composed of melanin granules. The concentration of pigment in the particular location of the Hudson-Stähli line can be explained by the sweeping massaging action of the lids, which would tend to compress these substances into a line projected on the cornea at the site of lid closure. The formation of such a line indicates some change in the character and re-

lationship of the corneal cells to one another and to Bowman's membrane. In these cases of hydroquinone exposure the appearance of such a line might well have been the earliest sign of the altered metabolism which led later to distortion of the cornea.

The origin and significance of the striae remains unexplained. They probably represent lines of optical discontinuity of a nature similar to the deep folds of the parenchyma seen in keratoconus and arise as a result of the difference in the coefficient of elasticity between the deep stroma and Descemet's membrane. They are, in other words, functions of internal tension within the cornea, a result of the puckering effect produced by the irregular contracture or stretching of the anterior corneal layers. Since they did not shift or change under pressure, these lines may actually have outlined spaces into which new corneal tissue of different density developed in a fault produced by this internal stress. The ultimate effect of this shift in the corneal lamella was the production of a flattening of the central corneal area. We might think of these changes as a double-faceted keratoconus, with the flattened surface lying between the two facets. The corneal thinning so characteristic of keratoconus was not uniformly present in these cases; neither were the striae so definitely related to the facets as in keratoconus. One could think of the process as a type of acquired cornea plana, since the principle feature of the fully evolved lesion was the flattened corneal curve with the high degree of astigmatism.

Summary and Conclusion

It is clear that the curvature of the cornea can be profoundly altered by exposure to quinone vapor or hydroquinone dust. These changes become apparent long after exposure, when the more obvious staining and pigmentation has disappeared. The chemical seems only to affect directly the most superficial layers of the cornea, the epithelium and probably Bowman's membrane. The first indication of this late effect is the appearance of Hudson-Stähli lines. The tension generated in the deeper parenchyma by the stretching or contracture of these superficial structures results in the deeper striae, which represent the second and more advanced stage in a process which ultimately leads to a flattening of the cornea or a double angulation which has some of the characteristics of keratoconus. These changes have resulted in the development of high degrees of astigmatism.

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The Role of Intraocular Pressure in the Development of the Chick Eye

IV. Corneal Curvature

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Introduction

The cornea of the adult vertebrate eye has a smaller radius of curvature than the posterior segment of the eye. In very early development, by contrast, the radii of curvature of the cornea and sclera tend to be equal. The manner in which the corneal curvature develops, and the forces responsible for it, are the concern of this paper.

The interplay of a large number of factors is undoubtedly necessary for the normal development of the corneal bulge. The present effort, however, was confined to an investigation of the role of mechanical forces generated, on the one hand, by intraocular pressure and, on the other, by structural differentiation of the eye wall. Previous studies in this series [1,2] have demonstrated that these forces are responsible for the increase in size of the eye as a whole as well as for the normal expansion of the sclera, choroid coat, pigmented epithelium, and corneal diameter. In addition, the normal morphogenesis of the ciliary processes and folds requires, among other things, a normally expanding vitreous.[3]

These studies have suggested that much of the gross shaping of the eye results from the interaction of intraocular pressure, which tends to expand the eye wall, with local retardation of expansion due to local structural differentiation in the wall. While such a conception of ocular morphogenesis is somewhat oversimplified, it has proven useful in suggesting possible mechanisms for the shaping of parts of the eye. Thus, it appeared possible that mechanical factors played a dominant role in the formation of the corneal bulge. This hypothesis has been tested, and the present paper presents both descriptive and experimental data in support of its validity.

Materials and Methods

This study utilized chick embryos of a Cornish-Rock cross which were incubated at 37.5 to 38.5 C in a forced-draft incubator. All ages are given as days following the onset of incubation.

The investigation was conducted in two stages, a descriptive and an experimental stage. The descriptive phase included the measurement of the corneal curvature and diameter during normal development and a histologic examination of the developing limbic area.

The following method was used to measure corneal curvature. On each day of the period between the 4th and the 24th days, inclusive, 10 eyes were dissected free of surrounding tissues, properly oriented in a pool of writing ink on the stage of a freezing microtome, and frozen. Eyes so prepared were hemisected through their optical axes with the freezing microtome. The remaining hemisphere was photographed at known magnification. The ink provided a constrasting field against which the outline of the hemisected eye stood out sharply. The negatives so obtained were next pro-

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jected at known magnifications, and the outline of the eye was traced on paper. On such tracings the radii of curvature of the cornea and the sclera were determined by geometric procedures.

The histology of the limbic area was studied in axial and equatorial sections of normal eyes fixed at daily intervals in Zenker's solution. These eyes were serially sectioned at 6μ and stained with hematoxylin and eosin.

A series of normal freshly dissected eyes, collected in groups of 10 at daily intervals throughout development, was used to measure the change in corneal diameter with age.

The role of intraocular pressure in the development of the corneal bulge was demonstrated experimentally. Microsurgical intervention at four days, before the appearance of corneal curvature, was used to reduce vitreal pressure. The procedure has been described in detail in an earlier paper.[1] One end of a short length of microcapillary tubing was introduced into the vitreous through a puncture wound in the wall of the right eye. The other end rested in the amnionic cavity. These tubes remained in place for the duration of the experiment, to provide continuous egress for vitreous humor. Eyes treated in this way were studied at 17 days of incubation. Ten eyes were frozen and hemisected for curvature measurements, and four were sectioned either axially or equatorially for histologic study.

As a control for the operative procedure, ten 4-day-old eyes were fitted with solid glass rods of the same outside dimensions as the tubes. Measurements of corneal and scleral curvature were performed on these eyes at 17 days.

Results

In the normal course of development the eye of the chick embryo is essentially spherical until the eighth day. The radii of curvature of the cornea and of the scleral segment are equal (Fig. 1). On the eighth day the corneal bulge becomes apparent,

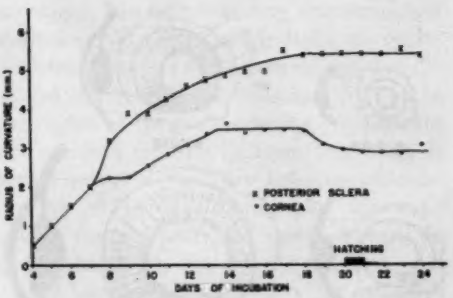

Fig. 1.—The radii of curvature of the posterior sclera and of the cornea as functions of age. Each point represents the mean of measurements of 10 specimens.

and thereafter its radius of curvature increases less rapidly than that of the sclera. The radius of curvature of the sclera continues to increase asymptotically throughout development. The radius of curvature of the cornea increases until the 14th day, remains constant between the 14th and 19th days, and on the 19th day decreases slightly to a new level.

In a search for events which correlate temporally and spatially with the appearance of the corneal bulge on the eighth day, histologic sections of a series of eyes were studied. This study confirmed the finding of Weiss and Amprino[6] that cartilage begins to differentiate in the chick sclera about the eighth day. In addition, it was possible to localize the site of first appearance of the scleral cartilage to a ring just outside the corneal limbus. Cartilage appears first in the presclera overlying the choroid fissure and subsequently spreads around the cornea to form a ring of pericorneal cartilaginous plates. Subsequent to the appearance of the ring this region of the eye surface expands less rapidly than the corneal portion anteriorly and the prescleral regions posteriorly. As a result, the eye subsequently expands not as a sphere but as the segments of two spheres with a common base (Fig. 2).

The temporary cessation of change in corneal curvature which commences on the 14th day is correlated with an abrupt slowing in the rate of increase in corneal diam-

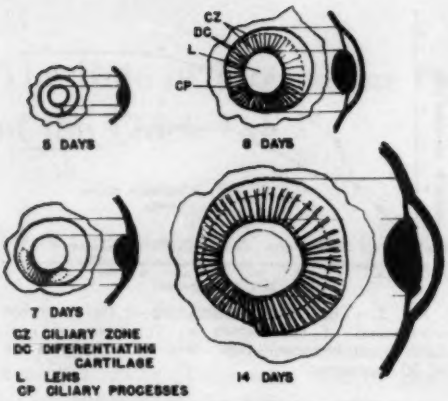

Fig. 2.—Diagramatic representations of the anterior segments of the right eyes of 5-, 7-, 8-, and 14-day-old chick embryos (to scale). A posterior view of the ciliary zone is represented at the left, and the silhouette of an axial section is shown at the right.

eter (Fig. 3). The significance of both of these changes will be discussed later.

The eyes which had been intubated at four days failed to increase in size normally.[1] The radii of curvature of the cornea and sclera tended to be equal in these cases (Fig. 4). Thus, while the ratio of corneal to scleral radius of curvature is normally about 0.6 at 17 days, it approaches 1.0 in the experimental group at this age (Fig. 5). In control animals the eye develops as if no operation had been performed and the ratio is essentially normal.

The level of differentiation of the ocular tissues in experimental eyes is comparable with that in normal eyes. As in previous studies, the intubation procedure distorted the size and shape of ocular components

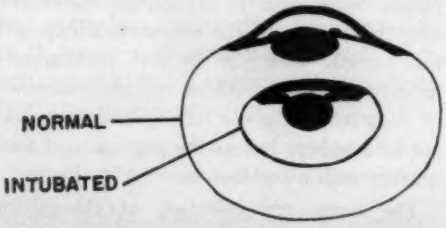

Fig. 4.—Silhouette diagrams of axial sections through a 17-day-old right eye that had been intubated since Day 4 and the contralateral, not-operated-on eye.

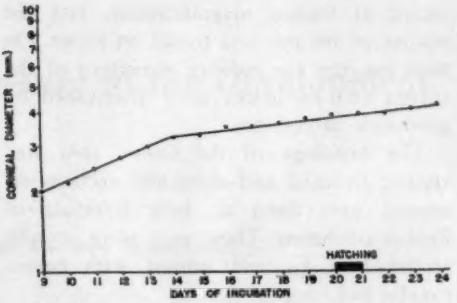

Fig. 3.—A semi-log plot of corneal diameter as a function of age. Each point represents the mean of measurements of 10 specimens.

without upsetting their timetable of cellular differentiation.

Comment

Many factors undoubtedly play a role in the shaping of the cornea. The present study has demonstrated that normal intraocular pressure is an essential but not a sufficient condition for the development of normal corneal curvature. In addition, there is evidence suggesting that corneal morphogenesis is influenced by the resistance to deformation that develops both around and in the cornea as a result of structural changes at the microscopic level. The operation of these forces and counterforces in

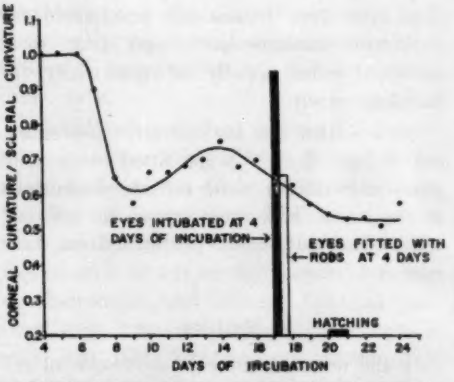
CORNEAL CURVATURE/ SCLERAL CURVATURE
EYES INTUBATED AT 4 DAYS OF INCUBATION
EYES FITTED WITH RODS AT 4 DAYS
HATCHING
DAYS OF INCUBATION

Fig. 5.—The ratio of corneal radius of curvature to scleral radius of curvature as a function of age. The black bar represents the mean ratio for 17-day-old eyes which had been intubated since Day 4. The white bar represents the mean ratio for 17-day-old control eyes, which had been fitted with solid glass rods since Day 4.

the molding of the cornea will be clarified in the following sequence, which is based on the results of this and of previous studies.

After formation of the optic cup and lens in early development, the edge of the cup becomes closely adherent to the lens equator. Thereafter vitreous humor begins to accumulate in the enclosure that is thus formed between the lens and the neural retina. The pressure generated by the accumulation of vitreous substance places the eye wall under tangential stress, and the eye expands as a sphere until the eighth day.[1,5] The fact that the eye expands spherically during this early period suggests that the resistance offered to expanding forces is approximately equal at all points on its surface prior to Day 8. During this period the radius of corneal curvature is equal to that of scleral curvature.

On the eighth day cartilage differentiates in the sclera to form a ring around the corneal limbus, dividing the eye into a smaller segment anteriorly (the cornea) and a greater segment posteriorly (the sclera). From the time of appearance of this ring of cartilage the limbic zone expands less rapidly than the remainer of the eye. As a result, the eye no longer expands as a sphere but approximately as the segments of two spheres with a common base through the limbic zone. Hereafter the radius of curvature of the anterior segment (cornea) is less than that of the posterior segment (sclera).

The cornea continues to increase in diameter and in its radius of curvature until the 14th day. The motive force for this expansion derives from intraocular pressure.[2] On the 14th day metachromatic mucopolysaccharide appears in the stroma and the stromal collagen becomes oriented and tightly packed.[3] Simultaneously the rates of increase of both the diameter and the radius of curvature of the cornea are slowed, as if the stromal differentiation had increased the resistance of the cornea to deformation.

One of the pivotal events of the eighth day, the differentiation of the limbic scleral cartilages, has an interesting counterpart in the mammalian eye, which lacks an ocular skeleton. Smelser * has pointed out that the scleral collagen of mammals appears first in the region of the limbus during development and spreads posteriorly from this ring. It seems probable that the collagenous components of the sclera may play the same role in mammalian ocular morphogenesis as does cartilage in the avian eye.

While intubation results in extensive disruption of the normal pattern of eye morphogenesis, it does not interfere with the timetable of cellular differentiation.

These findings give some insight into a few of the factors involved in shaping the cornea and sclera. They tell us little, however, about how the geometry of the cornea comes to be appropriately proportioned to the sclera in different species. That such a proportionate development does, indeed, occur is attested to by the fact that the adult cornea, by virtue of its shape and refractive properties, projects the visual image in focus in the near vicinity of the retina. For this to be so, the adult cornea must possess a radius of curvature and a diameter appropriate to the dimensions of the posterior segment of the eye. Without yielding a complete solution, this study has suggested several factors which will have to be considered in any attack on the problem of how this comes to be so. One such factor is the rate of accumulation of the vitreous body and the time course of development of forces tending to expand the eye. On the other hand, the timetable of cellular differentiation in restricted areas of the eye wall will act to restrict expansion differentially and to affect eye size and shape. It may well be that genic influences are mediated by control of the timing and magnitude of these events in eye development.

Summary

Under the influence of intraocular pressure the eye expands as a sphere until the eighth day. At this time scleral collagen dif-

* Personal communication to the author.

ferentiates in a ring around the corneal limbus and the perilimbic area thereafter expands less rapidly. This leads to the production of a corneal bulge anteriorly and a scleral bulge posteriorly. At 14 days metachromatic mucopolysaccharide appears in the stroma, stromal collagen becomes oriented and compact, and there is an abrupt slowing of the increase in both corneal diameter and radius of curvature. This formulation of the sequence of events is supported by both observation and experiment.

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Cyclodialysis with Air Injection

Technique and Results in Ninety-Four Consecutive Operations

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Division of the ciliary body from its insertion to the scleral spur as a surgical procedure in the control of glaucoma was employed sporadically prior to 1900. Following the original description of cyclodialysis by Heine,[1] in 1905, numerous variations in technique have been introduced. These variations include cyclodialysis with iridectomy, sclerectomy, or iridencleisis and the introduction of foreign material in the dialysis in an effort to maintain an open cleft. An excellent review of the literature regarding these and other variations of technique has been made by Sugar.[2]

The technique of cyclodialysis described by Heine includes preparation of a small conjunctival flap 8 to 10 mm. from the limbus in one of the outer quadrants and a scleral incision, 3 mm. long, parallel to and 6 mm. posterior to the limbus. The spatula is introduced between the choroid and sclera and passed forward to enter the anterior chamber; the attachment of the ciliary body is then divided from the scleral spur by sweeping the spatula from the chamber into the suprachoroidal space.

In 1935 Blaskovics[3] advocated a scleral incision just anterior to the insertion of the superior rectus, perpendicular to the limbus and 1.5 mm. in length. He advised inserting the cyclodialysis spatula nasalward within the suprachoroidal space before entering the anterior chamber, then separating the ciliary body from behind forward; the spatula is then withdrawn, reinserted in a temporal direction, and again swept forward into the anterior chamber.

The injection of air into the anterior chamber has been the most significant advance in cyclodialysis surgery in recent years. Randolph,[4] in 1943, described a cannulized cyclodialysis spatula which greatly facilitates the injection of air. Barkan,[5] in 1947, reported a series of 83 cases where air injection had been utilized, with a successful result in 69 of the cases. In 1949 O'Brien and Weih,[6] advocating the use of air injection and a multiple thrust technique, reported on a series of 100 cases with 79 successes.

The purpose of this report is to analyze the results of cyclodialyses with air injection in 94 operations for various types of glaucoma and to describe details of the technique we prefer to employ. The operative technique employed in the series of cases being reported upon involves the placement of the scleral incision beneath the insertion of the superior or inferior rectus muscle, the utilization of Randolph's cannulized cyclodialysis spatula, and the injection of air into the anterior chamber. We believe that the following features are of some importance in obtaining a successful result.

A. By having the incision placed in a slanting manner beneath the insertion of one of the vertical recti, the action of the muscle exerts a valve-like closure upon the scleral opening, effecting an excellent closure without suturing. Good closure of the scleral incision prevents a premature loss of the air bubble. With forceps, good fixation of the globe can be obtained by grasping the muscle tendon just behind its scleral insertion. Placing the cyclodialysis either directly

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superiorly or directly inferiorly, not crossing the horizontal meridian on either side, avoids rupturing either of the long posterior ciliary arteries and greatly reduces the incidence of profuse bleeding.

B. By use of a Randolph cannulized spatula attached to a syringe containing both saline and air, the anterior chamber can be continously reformed with saline as the dialysis is being made, thereby protecting the posterior surface of the cornea from damage by the tip of the spatula. The irrigation of saline also tends to clear the chamber of any immediate hyphema. Upon completion of the cyclodialysis, injection of air can be accomplished as soon as the saline is exhausted from the syringe. One-half to two-thirds of the chamber is filled with air. Care is taken not to inject so much air as to blockade the pupil. The Randolph cannulized spatula with the hole in the tip rather than on the superior surface just proximal to the tip is preferred. The spatula should be sufficiently flattened to obtain a dialysis without difficulty, and the tip should be rounded off and smooth.

C. The injection of air does not only exert a hemostatic effect; it is also of value in mechanically separating the anterior and posterior surfaces of the cleft. During the first three to four postoperative days, it is deemed advisable to keep the bubble floating up into the cleft much of the time. By the same means, any blood that may be present will tend to accumulate in the opposite side of the chamber by gravitation. When possible, it is preferable to do the cyclodialysis above. It is much easier and more comfortable for the patient to keep the head elevated rather than depressed.

D. A relatively large dialysis, between 130 and 160 degrees, is preferable. Air floats up into a large cleft much more readily than into a small one. Also, there is a tendency for partial closure of the cleft during the first few postoperative weeks, resulting in a permanent cleft much smaller than was present immediately after surgery. Lee and Allen [7] have reported a similar experience and emphasize that a large cyclodialysis is made not to obtain a large filtering space but rather to assure a small but functional cleft.

Preoperative Routine

Miotics are used routinely, and acetazolamide (Diamox) is employed when necessary to lower the intraocular tension to a safe level before surgery. Adequate sedation is obtained with barbiturates administered orally. Antibiotics are not employed prior to surgery.

The lashes are trimmed. Silver protein is instilled in the eye and is followed by copious irrigation with isotonic saline. The skin preparation consists of benzalkonium (Zephiran) solution followed by iodine and alcohol. Adequate anesthesia and akinesia are obtained by the injection of 4% lidocaine (Xylocaine) hydrochloride with 1:20,000 epinephrine, with use of the O'Brien technique and by retrobulbar injection.

Operative Procedure

A Parke lid speculum is inserted. The eye is turned downward if the procedure is to be done superiorly. Conjunctiva and Tenon's capsule are incised with scissors along either the medial or the lateral border of the superior rectus muscle. The insertion of the muscle is isolated and grasped with forceps and then everted slightly so as to expose the sclera just beneath the insertion of the muscle. An incision is then made through the sclera just beneath the insertion. This incision is approximately 2 mm. in length and is made so that it slants at approximately 30 degrees through the scleral stroma. Care is exercised in incising through the sclera so that the pars plana of the ciliary body is not penetrated. A Randolph cannulized cyclodialysis spatula is attached to a 5 cc. syringe containing approximately 1.5 cc. of saline and 2 cc. of air. The spatula is then introduced through the scleral incision and passed between the sclera and ciliary body; the tip of the spatula is kept pressed against the scleral surface at all

times to prevent accidental penetration of the ciliary body. The spatula is directed either nasally or temporally before sweeping into the anterior chamber. As the spatula enters the anterior chamber, saline is injected to maintain intraocular tension. Care is exercised to keep the tip of the spatula from pressing too firmly anteriorly just as the chamber is entered, to avoid stripping Descemet's membrane loose. The spatula exits from the chamber on the opposite side from its entrance, effecting a cleft averaging from 130 to 160 degrees of the angle. The remainder of the saline is injected, and then sufficient air is introduced into the chamber to fill approximately one-half to two-thirds of the chamber. The spatula is then withdrawn. The conjunctival incision is closed with 00000 plain absorbable surgical (gut) suture. The patient is asked to sit up immediately so that the air bubble will migrate up into the cleft. Physostigmine (Eserine), 0.25%, and phenylephrine (Neo-Synephrine), 10%, are instilled in the eye to obtain a tense iris diaphragm. A sterile dressing is placed over the eye, and a metal protector is placed over the dressing. The eye not operated on is usually covered.

Postoperative Care

The patient is allowed to be up as desired, and he is asked to sit in an upright position as much as possible during the first several postoperative hours. The head of the bed is kept elevated to approximately 45 degrees a majority of the time during the first three or four days so as to keep the air bubble up in the cleft. Erythromycin, 250 mg., and sulfamerazine 0.5 gm., four times a day, are prescribed for the first four postoperative days. The dressing is changed on the first day, and the eye not operated on is left uncovered. Miotics are not used routinely; in fact, the pupil is dilated with atropine if there is appreciable postoperative irritation.

When the cyclodialysis is done inferiorly, the immediate postoperative care is more difficult. Placing the head in a position so that the bubble will migrate into the cleft is uncomfortable for the patient, and the position cannot be maintained for long periods of time.

Analysis of Results

During the period between January, 1954, and July, 1956, cyclodialysis with air injection was utilized in the Henry Ford Hospital for surgical treatment of glaucoma in 94 instances; the procedure was repeated once in 2 cases and twice in another, a total of 90 eyes being operated upon. The cyclodialyses were performed by 12 surgeons, including both resident and permanent staff. The average hospital confinement following surgery was 9.5 days.

All cases are included in this review insofar as operative complications and immediate postoperative course are concerned. However, only those 84 operations with a minimum of three months' follow-up period are included in the evaluation of results obtained. The follow-up period for these 84 operations varies from 3 to 33 months, the average follow-up period being 15 months.

Criteria for "Success."—A result is termed successful only if the following requirements are met.

1. The tension must be controlled within normal limits, with or without the use of miotics. The 1954 revised tonometric scale is used, and the upper limit of "normal" is here considered to be 23 mm. Hg (Sklar). No absolute value is taken as the lower limit of normal, the delimiting criterion in an eye with low tension being whether or not there is hypotony such as to impair visual function.

2. There must be no progressive loss of visual field following surgery.

3. There must be no permanent and disabling injury to the eye as a direct result of the surgical procedure.

Results.—Classified according to these criteria, a successful result was obtained in 69 operations and failure was encountered in 19 (Tables 1 and 2). In analyzing the results obtained, the cases are grouped according to their etiology as follows.

TABLE 1.—*Results in Eighty-Four Cases with Follow-Up Periods of Three to Thirty-Three Months*

	"Success"	"Failure"
1. Primary open angle	47	5
2. Primary closed angle	6	1
3. Aphakic	11	4
4. Miscellaneous other	1	9
Total	65	19

TABLE 2.—*"Failures"*

	Tension Still Elevated	Tension Too Low	Retinal Detachment	Loss of Field
Primary open angle	2	1	1	1
Primary closed angle	1	0	0	0
Aphakic	2	1	1	0
Miscellaneous other	8	1	0	0
Totals	13	3	2	1

1. Primary Open-Angle Glaucoma: Cyclodialysis was performed in 57 instances in 56 eyes in cases classified as having primary open-angle glaucoma. The age of these patients varied from 36 to 85 years, the average age being 59. The average intraocular tension preoperatively while miotics were being used was 33 mg. Hg (Sklar). Visual fields changes were as follows:

	Cases, No.
Normal fields	9
Minimal field loss	24
Moderate field loss	10
Severe field loss	12
Not recorded	1

Aqueous outflow studies were performed in 45 cases; the outflow coefficient was below 0.13 in 39 cases and above 0.13 in 6 cases.

Results obtained with cyclodialysis in open-angle glaucoma were as follows:

	Cases, No.
Controlled without miotics	39
Controlled with miotics	8
Unsuccessful result	5
No follow-up	5

Each of the five unsuccessful cases is described in brief detail as follows.

CASE 1.—Following cyclodialysis, the tension remained between 30 to 42 mm. Hg (Sklar) over a 10-month period, with some progression of field loss. A second cyclodialysis was performed superiorly. After the second operative procedure the tension ranged from 8 to 18 mm. Hg (Sklar) without miotics.

CASE 2.—Preoperatively there was marked visual field loss, with retention of only a small temporal island of vision, and visual acuity was limited to counting fingers at 5 ft. The tension was markedly elevated and was not controlled after cyclodialysis. No additional operative procedure was performed.

CASE 3.—Preoperatively there was an immature cataract. Moderate hyphema was noted in the anterior chamber on the first postoperative day. On the sixth postoperative day the hyphema had cleared, but there was some vitreous hemorrhage and visual acuity was markedly decreased. The vitreous cleared slowly, and two months postoperatively a good red reflex could be seen superiorly; vision was limited to counting fingers. As the vitreous cleared, the cataract gradually progressed. About two and one-half months after surgery the patient noted a rapid drop in visual acuity in the operated-on eye. A cataract extraction was performed nine months after the cyclodialysis. A retinal detachment with marked retinitis proliferans and scarring in the posterior fundus could then be seen. It was felt that the retinal detachment was secondary to organization of vitreous hemorrhage.

CASE 4.—Preoperatively there was marked optic atrophy and loss of visual field to within 3 degrees of fixation. Tension was 50 mm. Hg (Sklar). The operative procedure and immediate postoperative course were uneventful. Examination two years after surgery revealed the eye to be blind. Tension was 8 mm. Hg at that time.

CASE 5.—This case was classified as an atypical open-angle glaucoma in which there was an anterior insertion of the iris root. Tension before surgery averaged 30 mm. Hg (Sklar) and was not adequately controlled with miotics. Early field loss was present. The immediate postoperative course was uneventful except for a mild anterior uveitis which cleared rapidly. The eye remained too soft, tension varying from mushy soft to 5 mm. Hg (Sklar). Edema of the macula resulted in gradual decrease of visual acuity to 20/70. Sixteen months after the

cyclodialysis an attempt was made to close the widely open cyclodialysis cleft by incarceration of iris into a scleral incision just posterior to the limbus in the area of the cleft. However, the iris failed to remain incarcerated. One month later, a second attempt was made to close the cleft. With use of a Grieshaber needle and 000000 black nonabsorbable surgical (silk) suture, a suture was placed through the sclera and ciliary body approximately 2.5 mm. posterior to the anterior edge of the ciliary body. The suture emerged 2 mm. from its point of entry. The suture was tied, and several surface diathermy applications were made just posterior to the suture. Gonioscopic examination revealed the cleft to be nicely closed. The silk suture was removed after six days. The cleft remained shallow after this procedure, with the posterior portion apparently completely closed, but not the anterior portion. The eye remained in hypotony for six months; then the tension suddenly rose to 34 mm. Hg (Sklar). After instillation of miotics the eye reverted to hypotony. During the past year there have been six episodes of acute rise in tension; on each occasion, the response to miotics has been rapid and the eye has reverted to hypotony, but the hypotony has gradually become less severe, visual acuity has improved, and the macular edema has largely subsided. During the periods of elevated tension, the eye becomes congested, the anterior chamber deepens appreciably, and the patient is aware of increased visual acuity.

2. Primary Closed-Angle Glaucoma: Cyclodialyses were performed in eight cases of narrow-angle glaucoma; seven of these cases were classified as chronic glaucoma, and one, as acute congestive glaucoma. In five of these cases, previous surgery had been performed without control of the tension (iridencleisis in four and cyclodialysis in one). Results are as follows:

	Cases, No.
Controlled without miotics	5
Controlled with miotics	1
Not controlled	1
No follow-up	1

The case in which the tension was not controlled was diagnosed as acute congestive glaucoma. Subsequent iridencleisis also proved unsuccessful.

3. Aphakic Glaucoma: Cyclodialyses were performed in 17 cases in which glaucoma developed following cataract extraction. The glaucoma in these eyes had resulted from various of the post-cataract-extraction causes of fibrous blockage of the angle. Operative results are as follows:

	Cases, No.
Controlled without miotics	11
Unsuccessful result	4
No follow-up	2

Unsuccessful results were encountered in four cases of aphakic glaucoma. Each case is discussed briefly as follows:

CASE 1.—Patient had had extracapsular cataract extraction with vitreous loss. There had been rapid development of a cyclitic membrane, persistent anterior uveitis, formation of anterior and posterior synechiae, and persistent corneal edema, and the intraocular tension had risen to 53 mm. Hg (Sklar). Five months after cataract surgery cyclodialysis was performed. The tension was not controlled.

CASE 2.—The patient had had an extracapsular cataract extraction three years previously. There were persistent corneal edema and an elevated intraocular tension of 40 mm. Hg (Sklar). Cyclodialysis failed to control the tension.

CASE 3.—Following cyclodialysis the patient has had a persistent hypotony. The tension has ranged from mushy soft to 5 mm. Hg (Sklar). Two years after surgery, the visual acuity now is 20/100; there still is persistent macula edema, and there is some definite macula degeneration.

CASE 4.—After cyclodialysis a moderate hyphema occurred on the third postoperative day, with slight reocurrence on the eighth postoperative day. As the hyphema cleared, examination revealed blood in the vitreous. The vitreous hemorrhage cleared slowly, but two months postoperatively there was sudden loss of visual acuity owing to retinal detachment. It is believed that the detach-

ment was secondary to organization of the vitreous hemorrhage.

4. Miscellaneous Other Types of Glaucoma: In this group of cases cyclodialyses were performed in 12 instances on a total of nine eyes. Results were as follows:

	Cases, No.
Controlled without miotics	1
Unsuccessful	9
No follow-up	2

A successful result was obtained in only one instance; this case exhibited broad anterior peripheral synechiae following intraocular foreign body.

The tension remained uncontrolled after three cyclodialyses on two eyes with glaucoma secondary to siderosis, in one eye with glaucoma secondary to penetrating injury, and in one eye with glaucoma secondary to persistent flat chamber following corneal transplant. Persistent hypotony resulted in one instance following cyclodialysis in a case of glaucoma resulting from intraocular foreign body and traumatic cataract.

In one eye with congenital glaucoma, cyclodialysis was employed on three occasions; previously, cyclodiathermy and several goniotomies had already proven unsuccessful. Sixteen months after the third cyclodialysis the tension was 24 mg. Hg (Sklar); the cornea has remained edematous and cloudy.

There are two aspects of the analysis of results which do not fit into the preceding discussion.

1. In the series of cases being reported, cyclodialysis was employed in 14 instances on patients of the Negro race. Adequate follow-up was not obtained in one case. In 12 cases of chronic open-angle glaucoma, a successful result was obtained in 7 cases without miotics and in 5 cases with miotics. One case of primary closed-angle glaucoma was successfully controlled with miotics postoperatively. It is interesting to note that miotics were necessary postoperatively in 6 of the 13 "successful" results (46%) in Negroes, in contrast to only 3 of the 52 "successful" results (6%) (Table 3) in white persons.

2. In this series of 84 operations with a follow-up of at least three months, six of the eyes had had unsuccessful iridencleises performed. In all of these, a successful result was obtained following cyclodialysis. Six additional cases had had unsuccessful cyclodialyses performed elsewhere; a successful result was obtained in five of these cases after repeated cyclodialysis.

Complications

Early complications included hyphema, vitreous hemorrhage, vitreous loss, and air blockade of the pupil (Table 4). Endophthalmitis did not occur in this series. Damage to Descemet's membrane was reported infrequently and apparently was of no serious consequence in this particular series; however, in the past, we have seen several instances where there was persistent corneal edema from stripping loose a large segment of Descemet's membrane.

1. *Hyphema.*—Hyphema occurring at the time of surgery was noted in 37 of the 94 cases; the hyphema was described as minimal in 25 and moderate in 12.

Hyphemas occurring between the 1st and 13th postoperative days were noted in 41 cases; most of these occurred during the 1st, 2d, or 3d postoperative day. The hyphema was described as mild in 24 cases, moderate in 14 cases, and severe in 3 cases.

Either immediate or delayed hyphema occurred in 68 of the 94 cases operated upon. The hyphemas, without exception, subsided

TABLE 3.—*"Successes"*

	White	Negro
Tension normal without miotics	49	7
Miotics required postoperatively	3	6
Totals	52	13

TABLE 4.—*Early Complications (Ninety-Four Operations)*

	Incidence, %
1. Hyphema	72
2. Vitreous hemorrhage	5
3. Vitreous loss	5
4. Pupillary block	1

spontaneously, without the necessity of surgical intervention.

Out of the 84 operations with at least a three-month follow-up, hyphema had been present in 51 of 71 instances (72%) where the tension was reduced to normal or below and in only 7 of the 13 instances (54%) where the tension remained elevated postoperatively. In this series, it would appear that the occurrence of hyphema had no definite influence on the control or lack of control of the tension postoperatively.

2. *Vitreous Hemorrhage.*—Blood in the vitreous was noted in five cases. In two instances in aphakic patients the source was thought to be infiltration of anterior chamber hemorrhage into the vitreous structure. In both of these, the blood gradually absorbed without damage to the eye. In one case where the vitreous hemorrhage was definitely attributed to poor surgical technique, the ciliary body having been penetrated with the spatula during the procedure, the blood likewise gradually absorbed without damage to the eye.

In two other instances it is not known with certainty whether the ciliary body was penetrated or not; in both of these cases the vitreous hemorrhage was followed by organization of the vitreous and retinal detachment.

3. *Vitreous Loss.*—Vitreous loss occurred in three aphakic eyes and in two phakic eyes. Follow-up examination was not obtained in one case. In three cases control of the glaucoma was successful, with no sequelae. In the fifth case, where the glaucoma was secondary to corneal laceration and traumatic cataract extraction, the tension remained elevated.

4. *Pupillary Block.*—Pupillary block occurred in one case on the second postoperative day. The tension was markedly elevated, and the air bubble was seen to completely cover the somewhat constricted pupil. Repeated instillations of 10% phenylephrine and 5% homatropine resulted in dilatation of the pupil with resulting relief of the air blockade and rapid return of tension to normal.

TABLE 5.—*Late Complications (Eighty-Four Operations)*

	Incidence, %
1. Tension elevated	15
2. Hypotony	4
3. Retinal detachment	2
4. Cataract	7
5. Pigment obstructing pupil	2

5. *Late Complications.*—Late complications include failure to control the intraocular tension, hypotony, retinal detachment, cataract formation, and iris pigment obstructing the pupillary space (Table 5).

(1) Tension Elevated: The tension remained elevated following cyclodialysis in 13 instances in a total of 10 eyes (the cyclodialysis had been repeated once in one case and twice in another without control). The tension usually became elevated during the hospital stay, and, with but one exception, the failure was evident within one month following surgery.

(2) Hypotony: Persistent hypotony occurred in three cases, as previously described. In three other instances the tension has ranged between 5 and 8 mm. Hg (Sklar) without evidence of decreased ocular function, and these have therefore not been classified as unsuccessful results.

(3) Retinal Detachment: The two cases having retinal detachment following organization of vitreous hemorrhage have been described in detail previously in this report.

(4) Cataracts: Progression of preexisting lens opacities or appearance of definite cataract formation frequently follows any type of glaucoma surgery. In this series cataract formation was definitely due to operative trauma in two instances. In four other cases there was rapid progression of the lenticular opacities, with marked loss of vision within six months after surgery. In nine other instances there were slow gradual lens changes which might or might not have developed more rapidly than would have been the case without surgery.

(5) Obstruction of Pupillary Space: Obstruction of the pupillary area by iris pigment on the lens capsule occurred in two cases. In both of these cases cataracts developed rapidly.

Summary and Conclusions

A series of 94 consecutive cyclodialyses employed in the surgical treatment of varied types of glaucoma has been reviewed, with emphasis being placed upon the evaluation of results obtained and complications encountered. The operative technique employed has been described in detail.

The indicated role of a specific operative procedure in the surgical treatment of glaucoma is always controversial and often somewhat cyclical. At present, cyclodialysis appears to be widely favored for aphakic glaucoma but only occasionally favored for other types.

In this series of cases cyclodialysis has given rather good results in chronic simple glaucoma, in chronic noncongestive narrow-angle glaucoma, and in aphakic glaucoma. Cyclodialysis would appear to be the surgical procedure of choice in those cases in which a filtering type of operation has proven unsuccessful. Because of the frequency of failure of the filtering operations in the Negro race, we feel that cyclodialysis is the indicated procedure in most cases of glaucoma in this group of patients.

The results were poor in the few instances where cyclodialysis was utilized for congenital glaucoma, for glaucoma secondary to siderosis bulbi, for glaucoma secondary to perforating injuries, and for primary acute congestive glaucoma.

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The Electroretinogram as a Prognostic Aid in Retinal Detachment

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In retinal detachment the amplitude of the b-wave of the electroretinogram (ERG) has been observed to be characteristically reduced. It has also been found that a reduction in amplitude of the ERG is usually also present in the opposite eye of the patient with the detachment. This has been reported, by investigators all over the world, during the past 10 years.[1-9]

Recently, Rendahl [10] has published a follow-up article on his original series, bringing the total he has studied to 250 cases. The conclusions drawn in this paper are that there is a statistically significant difference in the amplitude of the ERG between those patients who had a "successful" operative result and those who did not. Because of the great variation in individual cases, however, it was felt to be difficult to assess prognostic value to the ERG in a particular case. The author also felt, however, that in cases where the decision concerning the advisability of surgery is difficult, the ERG provides a valuable added bit of information, especially where a poor prognosis to be adduced by ordinary clinical methods of study.

In this study and, indeed, in all of the studies published, the criterion for "successful" treatment of the detachment has been the achievement of an anatomical restoration, that is, the reattachment of the retina. It is our opinion that, since the ERG is a measure of retinal viability, it is much more likely that a correlation exists between the eventual return of visual function and the ERG than between the restoration of anatomical integrity and the electrical activity of the retina.

Over the past three years, therefore, patients at the New York Eye and Ear Infirmary have been studied with preoperative ERG's. Although the number studied does not approach that of the Rendahl series, it is felt that statistically significant conclusions can be drawn.

Technique

A total of 80 patients, both private and service, were surveyed two to five days prior to proposed surgery. The ERG was recorded by use of a contact lens electrode and a standard EEG machine. The stimulus light was a General Radio Strobolux, producing 3.2×10^6 candles. For the purposes of this report we shall discuss only the results with white light. The ERG's in the two eyes were recorded simultaneously. The following factors were recorded in each case: (1) sex, (2) age, (3) eye affected, (4) duration of detachment, (5) original or recurrent detachment, (6) preoperative vision, (7) type of surgery, (8) anatomical result two months after operation, (9) vision two months after operation, (10) ERG b-wave amplitude in affected eye, and (11) ERG b-wave amplitude in fellow eye.

The patients were operated upon by a number of surgeons, both resident and attending, by a variety of techniques. Of the 80 cases initially studied, 30 were excluded from the series, for the following reasons:

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TABLE 1.—*Collected Statistics on Fifty Patients with Retinal Detachment*

Case	Sex	Age, Yr.	Eye Affected	Age of Detachment, Days	Original or Recurrent	Preoperative Vision*	Type of Surgery*	Vision 2 Mo. After Operation	Reattached 2 Mo. After Operation	ERG Amplitude (b-Wave)*	ERG in Fellow Eye	Retinal Detachment
1	M	68	O. S.	4	O	H. M.	D & S	H. M.	No	X	165	Large bullous; superior temporal tear
2	F	51	O. D.	?	O	H. M.	S	H. M.	No	X	140	Large, superior temporal tear, diabetic, high myope
3	M	49	O. D.	6	O	H. M.	D	20/70	Yes	50	230	Large, superior temporal (heavily pigmented)
4	M	74	O. S.	30	O	20/70	D	20/30	Yes	125	X	Large, inferior temporal, no tear seen, other eye phthisical
5	F	61	O. S.	10	O	20/40	D	20/70	No	85	140	Large, superior temporal, 2 tears, old aphakic detachment in fellow eye
6	F	60	O. S.	200	R	H. M.	D	H. M.	No	X	X	Entire temporal retina, aphakic O. U.
7	F	55	O. S.	9	O	20/100	D	H. M.	No	X	125	Superior, inferior, and nasal retina with tears, totally detached 6 mo. later
8	M	39	O. S.	4	O	20/400	S	20/400	No	X	90	Superior half of retina with multiple tears, high myope, aphakic
9	M	63	O. D.	40	O	H. M.	D	L. P.	No	X	140	Half retina, diabetic, aphakic O. U.
10	M	63	O. D.	12	O	20/200	D	20/70	Yes	65	145	Superior third of retina with tear
11	M	65	O. D.	10	O	20/70	D	20/200	No	215	75	Inferior third with tear, redetached three times
12	M	70	O. S.	400	O	H. M.	D	H. M.	Yes	X	125	Superior third with tear; mature cataract obscures postoperative view
13	M	54	O. S.	60	O	L. P.	S	L. P.	No	X	X	Inferior detachment
14	F	23	O. D.	100	O	20/70	S	F. C.	Yes	X	100	Inferior nasal with disinsertion; macular lesion
15	F	43	O. S.	5	O	H. M.	D	20/100	Yes	50	200	Superior temporal two-thirds with tear, moderately high myope
16	M	45	O. U.	?	R	H. M.	S	H. M.	No	X	X	Recurrent detachment O. U.
17	M	50	O. D.	9	O	20/200	D	20/50	Yes	200	200	Superior temporal half with macula involved
18	F	56	O. D.	20	O	20/30	D & S	H. M.	No	75	100	Superior third with tears
19	M	38	O. D.	17	O	H. M.	S	H. M.	No	25	200	Old organised detachment inferiorly with new detachment above
20	F	44	O. D.	7	O	20/25	D	20/20	Yes	70	115	Inferior half
21	M	60	O. D.	7	O	H. M.	D & S	H. M.	No	75	175	Superior third, aphakic O. U.
22	F	36	O. D.	10	O	20/100	D & S	H. M.	No	35	150	Superior temporal half with tears, 2 operations, totally detached after each, pathological myopia
23	M	15	O. D.	4	O	20/20	D	20/20	Yes	85	175	Superior temporal third with small holes and tear, trauma to the eye 4 days before operation

24	M	65	O. S.	14	O	H. M.	D	20/50	Yes	35	225	Superior half
25	F	57	O. S.	200	R	H. M.	S	H. M.	No	X	Normal	Total detachment, aphakic
26	F	52	O. S.	60	O	20/500	D & S	20/500	Yes	X	175	Inferior third
27	M	53	O. S.	30	O	H. M.	S	20/2000	Yes	25	250	Annular detachment with many fixed folds; trauma 2 mo. before operation
28	M	45	O. U.	10	R	H. M.	D & S	H. M.	No	X	X	Recurrent detachment O. U.
29	M	40	O. S.	100	O	20/1000	S	20/100	No	80	125	Complete detachment with tear
30	F	35	O. S.	14	O	20/50	D	20/50	Yes	80	90	Superior temporal with tears
31	F	20	O. D.	150	O	F. C.	S	20/70	Yes	75	250	Inferior half multiple holes, disinsertion
32	M	58	O. D.	?	O	L. P.	S	20/70	Yes	210	210	Full inferior detachment, aphakic
33	M	59	O. S.	40	O	H. M.	S	H. M.	No	X	85	Traumatic detachment involving macula, old folds
34	F	49	O. S.	40	R	20/400	S	20/200	Yes	X	150	Total, aphakic O. U., previous diathermy without success, hole near macula
35	M	65	O. S.	14	O	L. P.	S	20/50	Yes	90	200	Temporal third with tear
36	M	40	O. D.	60	O	L. P.	D & S	Nil	No	X	--	Temporal half with tear, choroiditis O. U., recurrent total detachment after previous operation
37	M	64	O. S.	4	O	F. C.	D & S	H. M.	No	75	125	
38	F	64	O. D.	50	O	F. C.	D & S	F. C.	No	125	--	Inferior third
39	F	49	O. S.	20	O	20/200	S	20/70	Yes	90	175	Superior temporal retina with tear
40	F	65	O. D.	?	O	H. M.	S	H. M.	No	X	X	Total, funnel-shaped, aphakic O. U.
41	F	40	O. D.	400	O	20/200	S	20/200	Yes	65	195	Temporal and inferior half with tear, old chorioretinitis
42	F	50	O. D.	30	O	L. P.	D	20/40	Yes	175	175	Inferior half with disinsertion
43	F	45	O. S.	16	O	L. P.	S	L. P.	No	25	110	Total with tear, fundus not seen after operation;—23D. O. U.
44	M	18	O. S.	60	O	20/200	D & S	20/25	Yes	100	225	Superior third with disinsertion, multiple head traumata —boxer
45	F	15	O. S.	3,000	O	20/1000	S	20/400	Yes	80	220	Inferior half with fixed folds and disinsertion
46	F	40	O. D.	30	O	20/400	D & S	20/50	Yes	50	220	Inferior half, high myope O. U.
47	M	74	O. S.	60	O	20/1000	S	L. P.	No	X	250	Total, half flat, half bullous
48	M	54	O. S.	5	O	H. M.	S	20/40	No	150	400	Temporal third with cysts and tear, high myope O. U.
49	M	49	O. D.	20	R	20/200	D & S	20/50	Yes	55	25	High myope; detached 3 yr. before with H. M.
50	M	48	O. S.	1,100	O	H. M.	S	H. M.	Yes	35	350	Probably traumatic, detachment at least 3 yr. old, total inferior half

* H. M., hand movements; F. C., finger counting; L. P., light perception; X, extinguished; D, diathermy; S, scleral resection.

	Cases, No.
No surgery performed	14
Insufficient data (including unreliable ERG)	14
Malignant melanoma	1
Albinotic aphakic with complex refractive and corneal disease	1

Results

The mean b-wave amplitude of the 50 cases was 52.3μv. (microvolts), as compared with 149.9μv. in the fellow eye and approximately 250μv. in our control series of 500 normal eyes.

The correlations between the ERG amplitude and the results of surgery were drawn in a number of ways, in order to coincide with published series and also to elucidate our own points.

The mean b-wave amplitude in those eyes in which anatomical restoration was achieved was 72.4μv.; in those eyes which did not have a satisfactory anatomical result the mean b-wave was 38.6μv. The difference between the means, 33.8μv., with a standard error of 16.2μv., is statistically significant at the 5% level.

The correlation between the ERG amplitude in a given eye and the eventual visual result was drawn in two ways. The mean b-wave of those eyes which attained a vision of better than 20/200 was 96μv. In those in which a vision of 20/200 or less was attained, it was 28.5μv. The standard error of the difference between the means is 14.2μv. This difference is significant at a level greater than the 1% level. A correlation of these two factors, the ERG amplitude and the postoperative visual result, was also drawn by the "rank difference" method. This statistical technique is a sensitive test of the existence of a correlation between an individual's standard in each of two achievement factors. The correlation factor, ρ, for this study, that is, a correlation of the amplitude of the ERG and the visual result, is 0.70, which is highly significant, indicating that there is almost no possibility of these findings being due to chance.

A calculation was made also of the relationship of the amplitude of the ERG of the fellow eye to the anatomical and visual result in the eye with detachment. In this series we eliminated those eyes which had a detachment or other serious pathology in the fellow eye. The mean of the fellow eye of those cases with an anatomical restoration was 185μv.; that of those fellow eyes in cases without anatomical restoration, 128μv. The difference, 57μv., is significant at the 5% level. Similarly, the mean of those fellow eyes in patients whose vision was 20/200 or worse was 129.8μv.; that of those with vision better than 20/200, 184.3μv. The difference in this case, 54.5μv., is also significant at the 5% level.

Aside from the statistical approach, several interesting observations can be made.

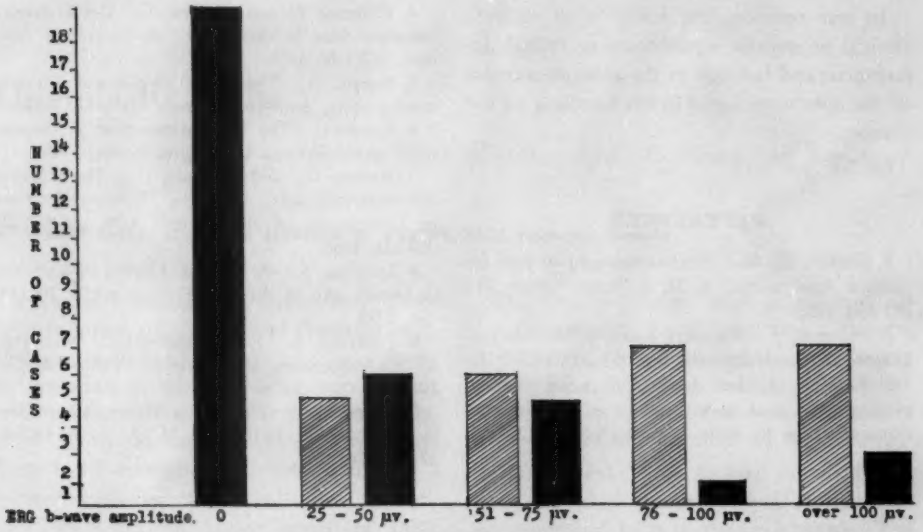
None of the patients in this series whose preoperative ERG b-wave was "extinguished," or below that capable of measurement by our techniques, attained a postoperative visual acuity of better than 20/200.

Of the patients who attained an anatomical reattachment, four had an extinguished ERG; none of these had a restoration of better than 20/200 vision. Table 2 presents those cases who had an anatomical restoration, in ascending order of ERG amplitude. Aside from the four cases with extinguished ERG's, Cases 27, 41, 45, and 50 had a visual result less than 20/200. Case 27 had the lowest measurable ERG, 25μv., and each of the other three had had their detachments for over a year. In our opinion this prolonged separation of the retina from its choroidal blood supply makes visual recovery doubtful.

Summary and Conclusions

The results of this study show that in 50 cases of retinal detachment the preoperative ERG b-wave amplitude bore a direct correlation of a high degree of statistical significance to the postoperative visual result and, to a less degree, to the reattachment of the retina as a consequence of surgery.

In no instance where the ERG was "extinguished," that is, below the limits of the



Distribution of patients according to b-wave amplitude and visual result, showing that none of the patients with an extinguished ERG attained vision of better than 20/200 and showing the proportion of visual results in patients with other ERG amplitudes. Black bar, visual acuity after surgery of 20/200 or less; hatched bars, visual acuity after surgery of better than 20/200.

TABLE 2.—*Patients Who Attained Anatomical Restoration of Retina, in Ascending Order of ERG b-Wave Amplitude*

Case	b-Wave	Postoperative Visual Acuity
12	X	H. M.
14	X	F. C.
26	X	20/500
34	X	20/200
27	25	20/2000
24	35	20/50
50	35	H. M.
3	50	20/70
15	50	20/100
46	50	20/50
49	55	20/50
10	65	20/70
41	65	20/200
20	70	20/20
31	75	20/70
30	80	20/50
45	80	20/400
28	85	20/20
35	90	20/50
39	90	20/70
44	100	20/25
4	125	20/30
42	175	20/40
17	200	20/50
32	210	20/70

ability of our recording technique to detect a response (about 15μv.), was a visual acuity of better than 20/200 attained. Of the few cases where reattachment was achieved and the ERG amplitude was "extinguished," none obtained vision of better than 20/200. Obversely, in those cases where restoration of the anatomical position was accompanied by vision of 20/200 or less, all had either extinguished ERG's or ERG amplitude of extremely low degree, with the exception of three cases in which the detachment had been present for at least a year prior to therapy.

A study of the prognostic significance of the ERG in retinal detachment must, in our opinion, consider not only the restoration of anatomical position of the retina but also the resumption of visual functional ability as a criterion of success. Since the ERG is a measure of retinal viability, and hence functional ability, we feel that consideration of this functional integrity is of prime importance.

Since, of necessity, in such a complex subject as retinal detachment and its therapy, a great number of variables must be considered, including the type of surgery, the propriety of the surgery, the skill of the individual surgeon, the postoperative course, and the duration of the disease, a statistical approach is an inescapable eventuality. The statistical analysis of these figures has, therefore, been as thorough as possible.

In our opinion, the ERG is of definite clinical prognostic significance in retinal detachment and belongs in the armamentarium of the ophthalmologist in his handling of the disease.

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Lipemia Retinalis

Report of a Case in a Diabetic Child Aged Twenty-Eight Months and Review of the Literature

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Lipemia retinalis is a visible ophthalmic manifestation of a profound disturbance in lipid metabolism. It occurs most frequently in association with diabetes concomitant with acidosis of a more or less severe degree. Only an ophthalmologist who has been lucky enough to see the fundus of a patient with lipemia retinalis can appreciate Heyl's [1] astonishment when, in 1880, he described its "remarkable appearance" for the first time.

The case of a 28-month-old boy presented here shares with that of Koch and Strong [48] the distinction of being the youngest diabetic with lipemia retinalis reported to date.

Case History

A white boy, aged 28 months, was admitted to the Montreal Children's Hospital on Oct. 9, 1956. He had been well until three weeks prior to admission, when easy fatiguability and refusal to play were noted. A week later it was realized that his appetite, previously exceptionally good, had diminished, although he was thirsty and drank up to 2 qt. of orange juice daily. He was weak and lethargic and had deep sighing respirations not associated with respiratory difficulty. He lost weight rapidly and became progressively more lethargic until the day of admission, when he became difficult to arouse.

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The family history was noteworthy in that the maternal grandfather was a diabetic at the time of his death and the mother was said to have developed diabetes at 16 years of age, which was cured spontaneously after 4 years of treatment by diet alone.

The patient's past history revealed that birth and development had been normal and that there had been no major illnesses. The weight at birth had been 7.5 lb., and prior to the present illness it was 38 lb. He was an only child.

On physical examination the child was pale, stuporous, emaciated, moderately dehydrated, and markedly hyperpneic. His weight was 22.2 lb. The liver was grossly enlarged, reaching almost to the umbilicus. The reflexes were diminished.

The external eye examination showed a low intraocular tension (digital). The pupils were dilated but reacted to light.

The fundus examination revealed all the characteristics of marked lipemia retinalis equally in the two eyes. The discs were a creamy yellow-pink, and the vessels on the disc and extending out into the periphery of the retina were ivory-colored. Arterioles and venules all looked alike and appeared flat and about twice the normal width. The retina itself was a pale yellowish-pink; there were no hemorrhages or other signs of pathological change. The visual acuity was not assessable because of his age and the presence of coma.

The urine examination revealed the presence of large quantities of both sugar and acetone. Blood withdrawn for biochemical and hematological analyses had the appearance typical of pronounced lipemia. It was

pale pink, and following centrifugation the supernatant plasma was found to be the color and consistency of cream. The hemoglobin could not be determined because of the turbidity; however the red cell count revealed an extreme degree of anemia (1,700,000 cells per cubic millimeter). The biochemical findings showed a profound acidosis with extremely low serum potassium, hyperglycemia, and hyperlipemia.

During the first 24 hours of treatment (Day 1) the child received 55 units of insulin in divided doses together with 500 mEq. of sodium and 100 mEq. of potassium. In addition, 200 ml. of plasma and 100 ml. of blood were administered. Intravenous therapy was continued during Day 2 together with divided doses of crystalline insulin. Some oral fluids were taken. By Day 3 the child was no longer in acidosis.

The total plasma lipids on Day 1 amounted to 16.0 gm/100 ml., and the plasma total cholesterol was 1.0 gm/100 ml. Electrophoresis of the plasma showed most of the fat to be neutral fat with low mobility. On Day 3 the total lipids had fallen to 11.7 gm/100 ml., and on Day 4, to 5.8 gm/100 ml. Clearing of the lipemia retinalis began on Day 3 and was first seen in the vessels of the disc, which began to assume a pinkish color in the center of the lumen while the walls remained pale; by Day 4 the pink color of the vessels extended out beyond the disc margin for 1 D. D. and the general appearance of the retina became less yellowish. On Day 5, the central vessels of the disc and for a distance of about 4 D. D. beyond were almost normal; the venules appeared purplish and the arterioles reddish, and both were of nearly normal caliber; however, the peripheral vessels were still lipemic. Between Day 6 and Day 7 the peripheral vessels cleared and the whole fundus became almost normal in appearance. From the slope of the disappearance curve, we would estimate that the blood lipids at this point were between 4.0 and 3.0 gm/100 ml. On Day 9 the plasma lipids were 1.8 gm/100 ml. and the fundi appeared completely normal. They have remained normal since. There was a steady improvement in the anemia, so that by Day 9 the hemoglobin was 8.9 gm/100 ml. and by Day 16 the hemoglobin had reached a normal level of 13.0 gm/100 ml.

The child was unhappy in hospital, had a poor appetite, and was weak and lethargic. It was finally decided that he would do better at home. He was accordingly discharged on Oct. 26, 1956, to the care of his family physician.

When seen again in March, 1957, the child appeared to be in excellent health; his weight was 36 lb.; his color was good, and he was alert and active. His eyes appeared normal. His liver was no longer palpable, and his diabetes was well controlled on 15 units of isophane (NPH) insulin daily.

Comment

According to Heyl,[1] milky serum, or lipemia, was reported by Rollo as long ago as 1798 in a treatise on the subject written in London. Later reporters were Kussmaul and Virchow. Duke-Elder, in his "Text-Book of Ophthalmology,"[58] describes lipemia as "a condition wherein fat in an emulsified state is present in the blood to a degree which alters its appearance." On the basis of evidence of available material in 1936, he stated, "Diabetes is the only disease wherein the condition becomes sufficiently marked to be seen ophthalmoscopically in the retinal vessels as lipaemia retinalis." He cited one exception, a case of leukemia reported in 1922 by Wagener.[18] Since Wagener's case, there have been reported to date 12 additional cases of lipemia retinalis in nondiabetics [37,40-42,46,47,50,52,53,57]; one of these was in a one-year-old child.[42] Most recent writers agree that many cases of lipemia retinalis are missed or not reported; the total of reported cases to date (May, 1957) is 82, of which 69 were diabetic and 13 were nondiabetic. About three-quarters of the cases have been in males; the average age has been 25 years, with extremes running from 1 year[42] to 65 years.[45] This is be-

lieved to be the 70th reported case in a diabetic.

The clinical appearance of the retina is found to be similar by all reporters. The arteries and veins are flat and ribbon-like and almost impossible to distinguish from each other; they appear to be filled with "cream." In severe cases this yellow-white coloring of the vessels extends from the periphery to the center of the disc, but more commonly the vessels on the disc, and frequently those up to a distance of 1 D. D. from the disc margin, remain salmon-colored; the light reflex is lost or diffuse, and there may be yellowish-white stripes paralleling the vessels. In less severe cases the background of the fundus remains relatively normal in appearance, but in severe cases it becomes lighter in hue, presumably because of lipemia in the choroidal vessels.[2,27,35,36]

Prior to the use of insulin, in 1922, twenty-four cases of lipemia retinalis were reported.[48] With one exception,[2] all died in coma. If one estimates the severity of lipemia retinalis by the degree of creamy coloration of the vessels, then most of the very severe cases have been discovered in association with diabetic coma. Visual acuity is rarely grossly affected during the acute phase, and it returns to preattack level after recovery. An occasional report of a small retinal hemorrhage [16,36] occurring in conjunction with lipemia retinalis is the only known ocular complication. In conjunction with diabetes, xanthomata [23,25,28,43] have been reported, which rapidly disappeared with insulin therapy.

A review of the literature reveals many attempts to explain the phenomenon, but most authors agree that the physiopathologic factors are still inadequately understood. It was noted by early reporters that visible lipemia retinalis could not be exactly correlated with blood lipid levels.[59] There were conflicting reports, and McCann [21] actually reported the disappearance of lipemia retinalis as total blood fat level rose. Blood lipid levels in lipemia retinalis have been reported ranging from 3.5 gm/100 ml. to 48.0 gm/100 ml.[4,7,10,20,27,28,33,59] Parker and Culler [30] believe that this variance is due to the multiplicity of methods used in lipid determination; they say that lipemia retinalis is apt to appear when the blood lipids rise above 3.5 gm/100 ml., while others [31,32,34] report clearing of the retinal vessels when the plasma lipids fall below an average level of 2.0 gm/100 ml.

The various explanatory theories for lipemia retinalis have been reviewed and may be summarized as follows.

Fatty infiltration of the perivascular tissues and vessel walls has been suggested by several writers [3,4,7,14,21,23,24,35,36,58] as a cause for lipemia retinalis. Muscle biopsies from patients with lipemia retinalis have shown fat in the vessel walls and perivascular lymph vessels, and it has been assumed that similar conditions probably prevail in the retina and that the normal or usually slight permeability of the blood capillaries to fat is in some way increased in lipemia retinalis. In Allen and Howard's case,[36] the appearance of lipemia retinalis persisted for two days after the blood fat levels had fallen to normal, supporting this theory.

Manning et al.[54] demonstrated the presence of fat-filled histiocytes in the bone marrow during lipemia retinalis; these cells disappeared when the blood lipids returned to normal; however, the lipemia retinalis disappeared while the fat-filled histiocytes were still demonstrable. They concluded that the presence of these cells could not entirely account for the eye changes.

Other authors have felt that hyperlipemia, perhaps of an unusual character, might of itself account for the phenomenon of lipemia retinalis. The nature of the lactescence and the factors causing it have been widely investigated. Marble and Smith,[35] in 1936, analyzed the plasma lipids in cases of lipemia retinalis and were able to show that the greatest proportional increase was in the fatty acid fraction, the next greatest

was in the cholesterol, and the least was in the phospholipids. They were able to show that the degree of lipemia does not necessarily parallel the degree of acidosis. Boyd,[60] in 1937, reported that in certain instances the lipid content of clear sera was higher than that of milky sera and showed that there was a quantitative relationship between the phospholipid level and the degree of lipemia. Ahrens and Kunkle,[61] in 1949, confirmed and extended these observations. Further elucidation of the physical phenomenon of lactescence of plasma was given by Albrink, Man, and Peters,[62] in 1955. They employed ultracentrifugation of the lipemic plasma to separate the insoluble fat particles so that a supernatant layer of fat and a subnatant clear plasma resulted. They found the clear subnatant plasma to contain neutral fat in solution between the limits of 10 and 30.4 mEq. per liter (0.27 gm. and 0.85 gm/100 ml.), although the total (soluble plus insoluble) neutral fat of the samples varied from 16.8 to 478 mEq. per liter (0.47 gm. to 13.9 gm/100 ml.). When the neutral fat increased above 20 mEq. per liter (0.56 gm/100 ml.), the serum was invariably lactescent. This increase in neutral fat was the only lipid change consistently associated with lactescence. Variations in phospholipid-fatty acid or phospholipid-cholesterol ratios were not apparently significant. It was their opinion that the primary metabolic block was in the removal of fatty acid from the plasma and that all other changes followed upon this.

From a physiological point of view, Stearns[49] points out that in diabetic acidosis there is a marked depletion of organic acid-soluble phosphorus in the blood cells which is accompanied by phosphaturia. With treatment of the acidosis the phosphaturia ceases, and there is a gradual replacement of the organic acid-soluble phosphorus in the cells, a process which takes about a week before normal levels are reached. This, he believed, indicated that one of the major metabolic defects in diabetic acidosis and in the associated lactescence of the serum was in the metabolism of organic phosphate compounds.

Thus, there is no adequate explanation for the development of lactescence of the plasma in certain persons. However, when this phenomenon does occur the plasma lipids have exceeded their limit of solubility and the excess lipids create the typical milky appearance of the plasma. The insoluble fat is present as chylomicra which, according to McCann,[21] vary in size from 7μ to 20μ in diameter. Chylomicra are demonstrable in normal plasma, but here the size varies from 0.035μ to 1μ. The large chylomicra of lactescent serum have been demonstrated in blood smears,[26] in capillary loops,[21] and in frozen sections of muscle biopsy specimens.[36]

As a corollary to Cohen's suggestion[16] that the lipemia retinalis might be due to the red blood cells congregating in the middle of the lumen, we should like to suggest that the phenomenon of lipemia retinalis can be explained at least in part by the physical relationship of the red blood cells and the chylomicra in the smaller blood vessels.

In all blood vessels the rate of flow of the blood stream is always most rapid in the center of the vessel and decreases toward the periphery. If to the blood stream is added a large number of chylomicra which are larger and less dense than the red cells, these fat particles will tend to move less rapidly and will be displaced peripherally. This will result in a vessel containing a central core of fast-moving red cells surrounded by a collar of slower-moving chylomicra. Seen from the side, such a vessel would appear whiter than normal. As one approaches the tertiary and quaternary branches of the retinal arterioles and venules, the average diameter of the vessels is 20μ to 25μ, at which point the chylomicra will arrange themselves linearly, since they may be up to 20μ in size. Under these circumstances, any preponderance of chylomicra over red cells will tend to reduce the red color of these

and smaller vessels. If anemia is marked, as in the present case, there may be such dilution of the red cells as almost to nullify any red coloration. This would explain why lipemia retinalis is seen first and last in the smaller peripheral vessels and in mild cases is confined to them. Thus, a rising red blood cell count and a decreasing lipemia would account for clearing of the lipemia retinalis. In future cases simultaneous chylomicron and red cell counts throughout the course of the illness would evaluate this theory.

Summary

A case of lipemia retinalis in a 28-month-old diabetic child is reported.

The literature is reviewed, and a complete list of references reported to date is presented.

A further explanation of lipemia retinalis based on the relationship of red cells to chylomicra is suggested.

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Constant-Pressure Tonography

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Scleral Rigidity in Tonography

It has been apparent to those working in tonography that one of the uncertainties of the procedure is the determination of the coefficient of scleral rigidity. This quantity, a characteristic of the individual eye, was formulated by Friedenwald [1] as follows:

$$E=\frac{1}{\Delta V_e}\log\frac{P_1}{P_2} \qquad (1)$$

in which

E=coefficient of scleral rigidity
ΔV_e=change of volume of the eye
P_1=initial intraocular pressure
P_2=final intraocular pressure

Grant [2] described the volume change in the eye during tonography. This may be expressed as follows:

$$\Delta V=\underbrace{\frac{1}{E}\log\frac{P_{t_1}}{P_{t_2}}}_{\text{(scleral shrinkage with drop in pressure)}}+\underbrace{V_{c_2}-V_{c_1}}_{\text{(increase in corneal indentation)}} \qquad (2)$$

in which

ΔV=total volume loss
E=coefficient of scleral rigidity
P_{t_1} and P_{t_2}=initial and final intraocular pressures with the tonometer in place
V_{c_1} and V_{c_2}=initial and final corneal indentation volumes [3]

Owing to the difficulty of measurement of E in the individual case, some workers have assumed an average value of E in their clinical work.

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In computation of the facility of outflow (Linnér's modification [4] of Grant's formula),

$$C=\frac{\Delta V}{t(P_{t_{AV}}-P_o-\Delta P_v)} \qquad (3)$$

in which

C=facility of outflow
t=time
$P_{t_{AV}}$=average tonometric pressure
P_o=intraocular pressure before instrumentation
ΔP_v=increase in episcleral venous pressure due to instrumentation

the value selected for P_o also depends upon estimation or assumption of E. P_o may be measured independently, as by the Goldmann applanation tonometer. The marked effect of variations in scleral rigidity on the determination of facility of outflow by tonography has been described by Friedenwald [3] and discussed exhaustively by Ballintine.[5]

Elimination of the Scleral Rigidity Factor in Tonography

If the pressure within the eye could be held constant during tonography, the scleral shrinkage term in Equation 2 would be eliminated, and

$$\Delta V=V_{c_2}-V_{c_1} \qquad (4)$$

The average value for P_t in Equation 3 would be replaced by a constant value. Equation 3 then becomes

$$C=\frac{V_{c_2}-V_{c_1}}{t(P_t-P_o-\Delta P_v)}=\frac{\Delta V_c}{t(P_t-P_o-\Delta P_v)} \qquad (5)$$

The necessity of estimating P_o and ΔP_v could be eliminated as follows: If two constant-pressure measurements were made at different pressure levels, facility of outflow would be

$$C=\frac{\frac{\Delta V_{II}}{t_{II}}-\frac{\Delta V_I}{t_I}}{P_{t_{II}}-P_{t_I}} \qquad (6)$$

in which subscripts I and II refer to the measurements at two different pressures.* This equation is graphed in Figure 1. The

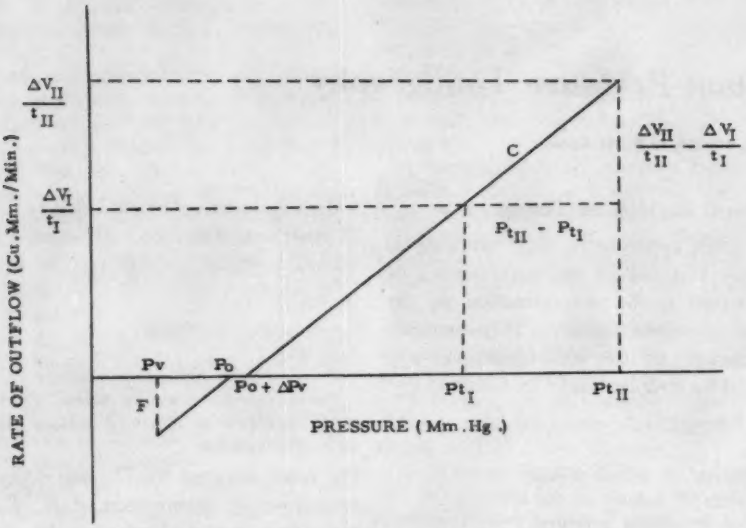

Fig. 1.—Graphic representation of Equation 5.

line of slope C would cross the pressure axis at $P_o+{}^{\Delta}P_v$*

$$*C=\frac{{}^{\Delta}V}{t(P_t-P_o-{}^{\Delta}P_v)} \text{ or}$$

$$P_o=P_t-\frac{{}^{\Delta}V}{Ct}-{}^{\Delta}P_v \qquad (7)$$

On tonographies I and II

$$P_o=P_{t_I}-\frac{{}^{\Delta}V_I}{Ct_I}-{}^{\Delta}P_v=P_{t_{II}}-\frac{{}^{\Delta}V_{II}}{Ct_{II}}-{}^{\Delta}P_v$$

$$P_{t_I}-\frac{{}^{\Delta}V_I}{Ct_I}=P_{t_{II}}-\frac{{}^{\Delta}V_{II}}{Ct_{II}}$$

$$\frac{{}^{\Delta}V_{II}}{Ct_{II}}-\frac{{}^{\Delta}V_I}{Ct_I}=P_{t_{II}}-P_{t_I}$$

$$C=\frac{\frac{{}^{\Delta}V_{II}}{t_{II}}-\frac{{}^{\Delta}V_I}{t_I}}{P_{t_{II}}-P_{t_I}}$$

F, the outflow of aqueous at normal intraocular pressure, would be calculated as usual from Goldmann's equation[5]:

$$F=C(P_o-P_v) \qquad (8)$$

Method

Some years ago Dr. Elmer Ballintine suggested to me that intraocular pressure might be maintained by adding weight to the tonometer plunger as fluid leaked out of the eye.

In the Friedenwald nomogram, at any constant pressure (scleral rigidity zero), plunger weight and scale reading are linearly related (Fig. 2). A separate isobar line can be drawn for each P_t value. Thus, if during tonography, as the scale reading increases, weight is added to the plunger at an appropriate rate P_t can be kept constant.

It was found by trial that if a line were drawn perpendicular to the Mueller tonometer scale reading 5.2, this line crossed the extensions of the other scale lines at nearly equal intervals from Scale 2 to Scale 14 (Fig. 3). A 1 cc. tuberculin syringe containing mercury was arranged parallel to this line of equal divisions so that the plunger could be depressed by a lever manually maintained at the position of the tonometer needle. The mercury was conveyed by fine tubing to the tonometer handle, where a nozzle of 23-gauge steel tubing was aimed at a small paper cup fastened to the end of the plunger (Fig. 4). Calibration was accomplished by adjusting the height of the syringe until the weight of the mercury expelled between the scale readings for two standard plunger weights at a given pressure level corresponded to the desired weight. The 1955 Friedenwald tonometry tables[6] were used as a basis for calibration.

In use, volume values for intermediate plunger weights are obtained by interpola-

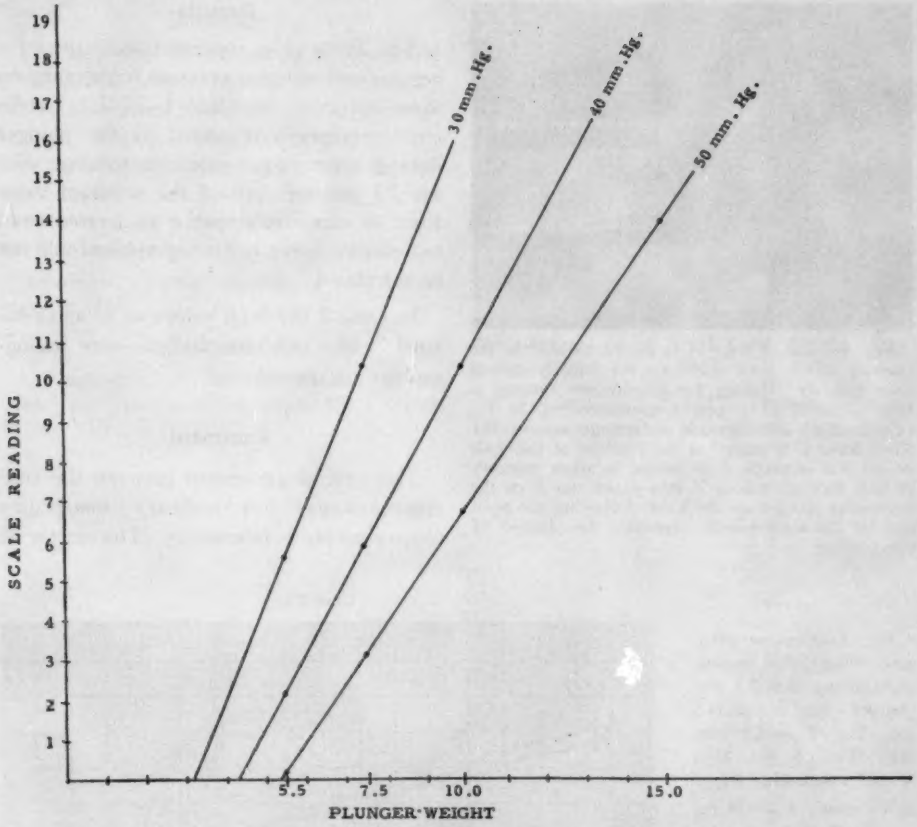

Fig. 2.—At constant P_t tonometer scale reading is linearly proportional to plunger weight.

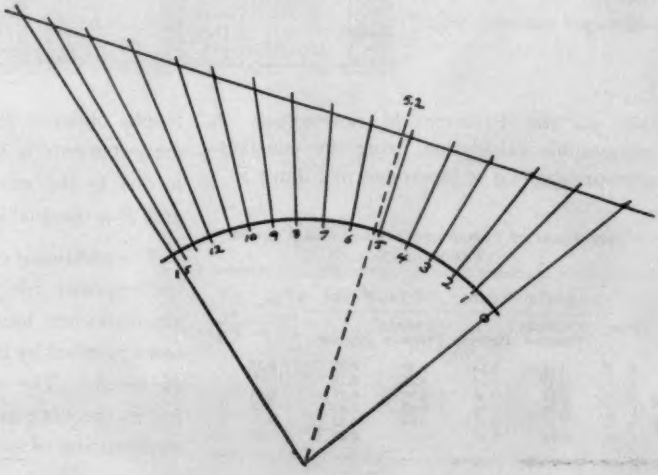

Fig. 3.—On the Mueller tonometer dial a line perpendicular to the line of the needle at Scale 5.2 is equally divided by the projections of the scale readings from 2 to 14.

Fig. 4.—The syringe *A* is placed parallel to the line on which scale divisions are equally spaced (see Fig. 3). During tonography the syringe is first adjusted to a height corresponding to P_t. (Calibrations are engraved on syringe support *B*.) Then lever *C* is placed at the position of the scale needle and stopcock *D* is turned to allow mercury to flow through tubing *E* into paper cup *F* on the tonometer plunger as the lever, following the position of the scale needle, depresses the plunger of the syringe.

Results

The Table gives representative values for regular and constant-pressure tonography on three subjects. In Case 1, L. E., insufficient mercury was added to the plunger during constant-pressure tonography with the 7.5 gm. weight and the resultant value for *C* is excessively low; *C* as derived from two constant-pressure tonographies could not be calculated.

In Case 2 the high values of *C* as calculated from two constant-pressure tonographies are unexplained.

Comment

The general agreement between the constant-pressure and ordinary tonography measurements is heartening. The scatter of results obtained from two constant-pressure measurements is unsatisfactory and in part is due to the small difference between P_{t_I} and $P_{t_{II}}$ obtainable with present methods.

The additional equipment and extra operator required for the performance of constant-pressure tonography do not at present seem justified by the questionable refinement of results. The method is presented here for its theoretic interest and for its essential confirmation of ordinary tonography.

Case 2

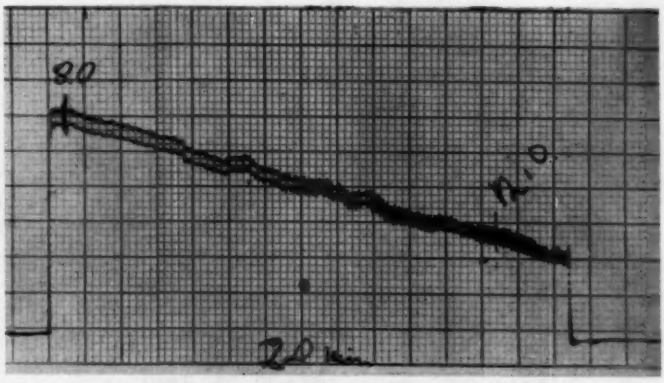

Fig. 5.—Constant-pressure tonography recording starting with 7.5 gm. plunger load. P_t=34.5 mm. Hg; P_o=15.6 mm. Hg; $^{\Delta}P_v$=1.5 mm. Hg; $^{\Delta}P$=17.4 mm. Hg; V_{e_1}=16 cu. mm.; V_{e_2}=24 cu. mm.; $^{\Delta}V$=8 cu. mm.; t=2.0 minutes. $C=\frac{^{\Delta}V}{^{\Delta}P \times t}=\frac{8}{17.4\times 2}$=0.23 cu. mm. per minute per millimeter Hg.

tion on the Friedenwald nomogram. A tonographic calculation using the constant-pressure method is illustrated in Figure 5.

Comparison of Constant-Pressure and Regular Tonography

Case		5.5 Gm. Weight		7.5 Gm. Weight		$\frac{\Delta V_{II}}{t_{II}} - \frac{\Delta V_I}{t_I}$ / $P_{t_{II}} - P_{t_I}$
		Constant Pressure	Regular	Constant Pressure	Regular	
1	R. E.	0.15	0.14	0.20	0.15	0.18
	L. E.	0.20	0.19	0.15	0.18	?
2	R. E.	0.24	0.26	0.26	0.27	0.51
	L. E.	0.22	0.29	0.23	0.31	0.43
3	R. E.	0.17	0.17	0.19	0.12	0.22
	L. E.	0.13	0.14	0.17	0.19	0.26

Summary

The necessity of estimating or assuming a value for scleral rigidity in tonography can be eliminated if the intraocular pressure be kept constant during tonography.

A method of keeping the intraocular pressure constant by adding weight to the tonometer plunger in proportion to the scale reading is described.

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Operating Room Gonioscopy in Angle-Closure Glaucoma Surgery

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It is now generally accepted that iridectomy is the most logical, the most effective, and the safest operation for the control of angle-closure glaucoma. Unfortunately, it is ineffective if the anterior chamber angles are occluded by permanent peripheral anterior synechias. The purpose of this paper is to present a technique for determining the presence or absence of synechias at the time of surgery.

When tension can be restored to normal by medical means within 12 hours in angle-closure glaucoma, conventional presurgical diagnostic methods can be employed. If gonioscopy shows that the angle has opened, one can be confident that iridectomy will be curative. If the angle still seems to be blocked, it is probable that the synechias are permanent and that the low tension is on the basis of suppression of aqueous production. This assumption can be proved or disproved by tonography. If the coefficient of aqueous outflow is high, the outflow channels must be patent, and it is probable that iridectomy will be successful.

When tension does not drop to normal, however, it is impossible to know if iris is permanently attached to the trabeculum or if it is only pressed against it. It is quite possible for permanent peripheral anterior synechias to form in an eye which has never had an attack of angle-closure glaucoma. Conversely, it is also possible for an eye to lose most of its vision from a chronic narrow angle glaucoma and yet to have the angle open almost completely following a simple iridectomy. Therefore, it is impossible dogmatically to assume the presence or absence of peripheral anterior synechias by the duration of the angle closure.

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In the past a filtering procedure has been advised if the tension in an acute attack has been elevated over 36 hours or if there has been any history of previous tension elevations. Such advice may be correct in the majority of cases. Unfortunately, the possibility of complications and the probability of decrease in vision is considerably increased by any of the external fistulizing operations. It is far better to employ iridectomy and the normal outflow channels if this is at all possible. This is the problem which has led to the adoption of gonioscopy in the operating room to enable the surgeon to make a logical decision.

In the glaucoma clinic at the University of California Medical School the following procedure is being followed in all cases of angle-closure glaucoma. First, a determined effort is made to bring down the tension by miotics, acetazolamide (Diamox), retrobulbar injections of procaine, etc. If the tension is falling rapidly after four hours, the medical regimen is continued. If pressure is normalized, surgery may be delayed one to two days to permit the eye to quiet down and to allow gonioscopy and tonography. If tension is not normalized, surgery is done within 12 hours.

At the time of surgery a beveled corneal paracentesis is made in the lower third of the cornea, with a Wheeler or Grieshaber knife-needle, so that the anterior chamber can certainly be re-formed postoperatively. A routine ab externo peripheral iridectomy is performed, following the technique of Haas and Scheie.[1] After the iris is reposited

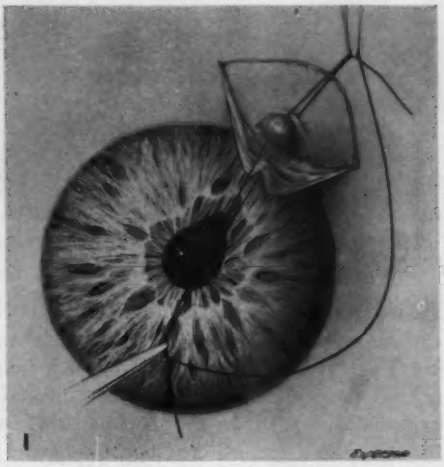


Fig. 1.—Peripheral iridectomy performed.

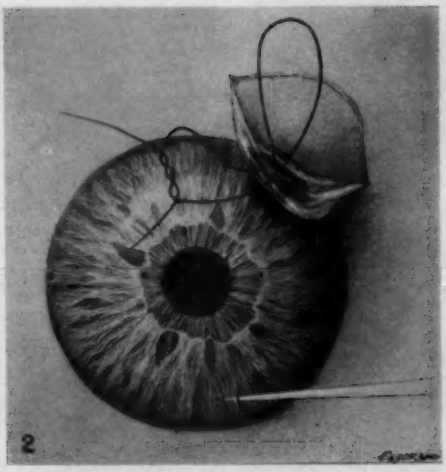
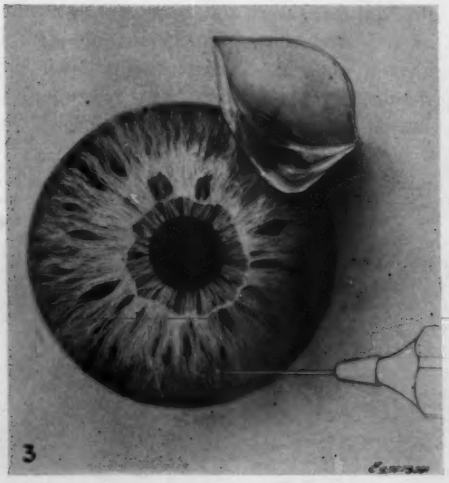


Fig. 2.—McLean suture with the first loop of a surgeon's knot. Beveled corneal incision for reforming chamber previously prepared.

with a stream of saline from an anterior chamber irrigator, the first half of a surgeon's knot is tied in the McLean suture and tightened. Usually the anterior chamber will have been filled by the irrigation. If the chamber has not formed, saline is injected through the corneal paracentesis.

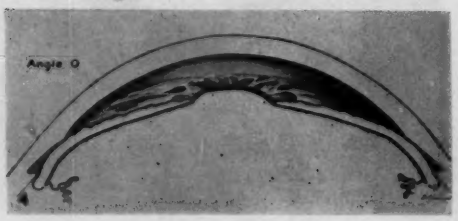
A sterile glass Koeppe diagnostic contact lens is then placed over the eye and filled with saline. The surgeon now drops out of the sterile set-up to examine the eye gonioscopically with a Barkan hand illuminator and a corneal microscope. The latter is best supported on a stand, but it may be handheld if equipment is not available.[2] The surgeon can now see the angles of the anterior chamber and tell at once whether or not peripheral anterior synechias are present. If the iris has dropped free of the trabeculum, the assistant completes the tie of the McLean suture, closes the conjunctiva, and dresses the eye. The patient is almost surely cured.

Fig. 3.—Incision closed. Chamber re-formed if necessary.



If the surgeon sees that extensive anterior synechias are present, several courses are open. A synechialysis, as suggested by Dr. Paul Chandler,[3] may be effective. A spatula is passed into the chamber through the original incision, and the synechias are dialyzed. This is useful if the synechias are in the upper half of the eye. It is difficult to reach the lower angle without possible dam-

Fig. 4.—Gonioscopy, showing cutaway drawing of closed angle.



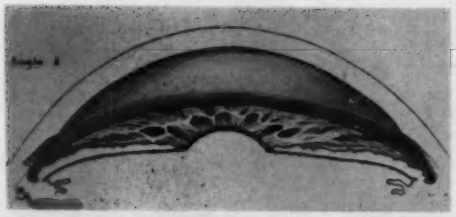


Fig. 5.—Gonioscopy, showing degree of opening of angle after iridectomy if no anterior synechias are present.

Fig. 6.—Gonioscopy after iridectomy, showing permanent anterior synechias.

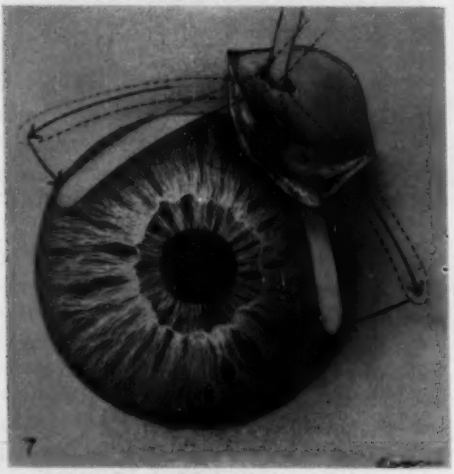


Fig. 7.—Cyclodialysis done near spur to free angle of synechias.

age to the iris and the lens. After reformation of the anterior chamber, the gonioscopy is repeated. Sometimes the synechias are still present, as the spatula may merely turn the iris under without actually freeing it from the trabeculum. When this occurs, an inverse cyclodialysis is indicated. This can be done through the original incision, but I prefer to make a second incision just behind the spur and do a routine inverse cyclodialysis so that the spatula can be brought into a formed chamber, thus avoiding damage to Descemet's membrane. Bleeding is avoided by keeping the spatula close to the spur and by restoring the intraocular pressure by saline injection as soon as the dialysis is completed. Even though a suprachoroidal cleft is not formed, the stripping away of the iris may give sufficient functioning angle to maintain normal pressures in the future. Miotic drops are often needed because of the damage done to the trabeculum when the iris has been in apposition with it for any length of time.

For the surgeon who prefers external filtration when peripheral anterior synechias are present, it is possible to convert the iridectomy into an iridencleisis by removing the McLean suture and incarcerating a pillar of iris after cutting the sphincter. If this is contemplated, a large conjunctival flap should be prepared before the iridectomy is started. I prefer to reserve iridencleisis for

Fig. 8.—Relation of cyclodialysis incision to iridectomy incision.

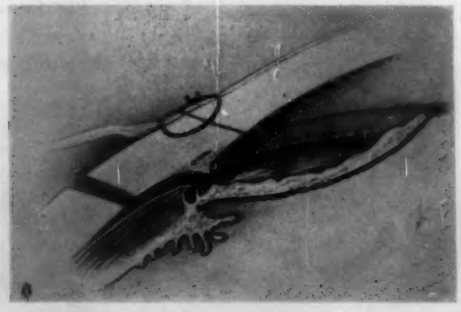
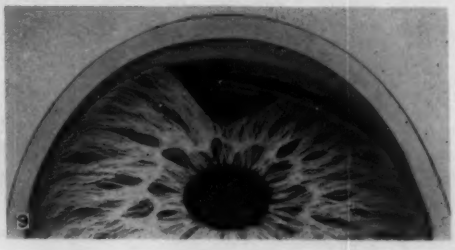


Fig. 9.—Gonioscopy after single-sweep cyclodialysis. Peripheral anterior synechias still present on opposite side.



those cases in which the procedures mentioned before have failed.

Postoperatively there is a strong tendency for posterior synechias to form. It is most important to dilate the pupil once a day for the first week or two. Phenylephrine (Neo-Synephrine), 10%, should be tried first, but use of atropine should not be delayed if dilation is not achieved. Despite the fears of some ophthalmologists, there is no danger of a rise in tension if a patent iridectomy is present.

In only two instances was it impossible to obtain a sufficiently clear view at the time of surgery to be sure whether or not the angle was open. In one of these there had been a small hyphema from bleeding of the iris root. The aqueous remained sufficiently turbid to preclude gonioscopy. In another there was marked corneal edema with wrinkling of Descemet's membrane which made gonioscopy difficult. In the other cases gonioscopy * was felt to be a distinct help.

* Dr. Paul Chandler[3] has effectively modified this procedure by performing the gonioscopy before the iridectomy. Through a bevelled corneal paracentesis, aqueous is completely evacuated, including that which has been trapped behind the iris. The anterior chamber is then reformed with saline and gonioscopy is done. The removal of posterior aqueous allows the iris to drop away from the trabeculum if permanent peripheral anterior synechias have not formed.

Summary

It is well known that an iridectomy may be ineffective in curing angle-closure glaucoma if permanent peripheral anterior synechias are present. In the past the choice of surgery has been based empirically upon the history of previous acute attacks or on the duration of the present attack. It is suggested that gonioscopy provides a method by which the presence or absence of peripheral anterior synechias can be determined on the operating table. A logical choice of surgery can then be made.

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Urinary Excretion of Citrate in Humans Following Administration of Acetazolamide (Diamox)

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Citrate is excreted in comparatively large amounts in human urine, and its excretion varies with age, diet, sex, and other factors from 100 to 1500 mg. per day.[1-4] It is lower in infants and children as compared with adults.[1-3,5-7] Citrate excretion is decreased by acidosis [7-12] (dietary, uremic, and diabetic) and by testosterone administration.[13] It is increased in alkalosis [7-12] and by the administration of estrogens,[14,15] parathyroid extract,[2,16,17] and vitamin D.[18-22]

Previous experimental and clinical studies have suggested that urinary citrate aids in the chelation of calcium into a soluble complex. Low citrate levels in the presence of normal calcium-phosphorous ratios may play a role in the formation of renal calculi.[2,23,24] In addition, citrate therapy has been reported to have induced an apparent improvement in a case of nephrocalcinosis.[25]

In rats, acetazolamide administration has been observed to result in the deposition of calcium phosphate in the tubules and pelvis of the kidney.[26] The experimental production of such lesions was accompanied by a marked decrease in urinary citrate excretion.

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Ureteral colic has been reported in patients receiving acetazolamide for periods of time.[27-31] The increased use of this agent in glaucoma therapy has resulted in the recognition of additional instances of this systemic side-effect. The recent observation of patients presenting symptoms of ureteral colic while taking acetazolamide therapy for glaucoma stimulated the present study, designed to determine whether citrate excretion is diminished in humans following the administration of this drug.

Methods

The subjects in this series were (1) 10 normal healthy volunteers, (2) 10 glaucoma patients taking long-term acetazolamide therapy, and (3) 20 glaucoma patients from the Washington University Glaucoma Clinic, 10 of whom were taking long-term acetazolamide therapy and 10 of whom were receiving therapy other than acetazolamide. All subjects were ambulatory, and no special dietary restrictions were imposed.

In the case of the 10 healthy volunteers, the 24-hour urinary citrate and calcium excretions were determined in control periods and immediately after the administration of a single oral dose of 250 mg. of acetazolamide. When the experiment was repeated in the same subject, an interval of one to three weeks was allowed between tests. A total of 48 control and acetazolamide collections of 24-hour urine specimens were thus obtained for comparison. In four of these the citrate content of each voiding was also determined, in order to learn about the duration of effect of acetazolamide. For the 10 patients receiving long-term acetazolamide therapy, 24-hour urinary citrate values were measured

TABLE 1.—*Twenty-Four-Hour Urinary Excretion of Citrate and Calcium in Normal Humans: Effect of Acetazolamide* *

Subject	Age, Yr.	Race	Sex	Control Periods			After Acetazolamide			Citrate Decrease, %
				Volume, Ml./24 Hr.	Citrate, Mg./24 Hr.	Calcium, Mg./24 Hr.	Volume, Ml./24 Hr.	Citrate, Mg./24 Hr.	Calcium, Mg./24 Hr.	
1	35	W	M	910	850	39	1,050	277	32	67
				1,200	696	27	1,400	193	51	72
				1,100	563	50	2,010	266	47	53
				1,250	786	35	1,850	185	42	76
2	40	W	M	910	437	20	975	95	18	70
				2,150	345	80	2,720	70	50	80
				2,000	600	47	2,150	55	60	91
3	35	W	F	1,150	846	80	1,800	360	62	57
				800	845	110	1,300	286	128	67
				950	665	104	1,250	385	101	59
4	30	W	M	1,425	722	58	2,100	399	95	45
				1,440	750	390	1,440	387	321	48
				1,200	556	91	1,500	360	110	35
5	29	W	M	1,625	272	70	1,750	104	56	62
				1,725	293	49	1,950	103	41	65
				1,200	156	112	1,400	87	120	45
6	22	W	M	1,450	323	90	1,900	143	104	56
				1,800	465	237	2,000	132	186	71
				1,200	620	232	1,800	151	260	76
7	22	W	F	1,500	323	150	1,600	138	130	57
				1,100	330	165	1,750	148	210	55
8	27	W	F	1,130	158	443	1,700	72	208	55
9	19	W	F	780	422	18	740	115	20	70
10	20	W	F	600	75	35	510	40	25	46
Mean				1,275	504	114	1,610	190	103	62±13

* Single oral dose of 250 mg.

on six occasions in one, three times in another, and once in each of the remaining eight. In the 20 glaucoma clinic patients the urinary citrate and calcium excretions were determined on random single urine specimens voided at the time of their clinic visit (2 p. m.).

Citrate in urine was determined by the method of Ettinger et al.,[32] and calcium, by the method of Carr and Frank.[33]

Results

In Table 1 are summarized the urinary citrate and calcium excretion data obtained both before and after the administration of 250 mg. of acetazolamide in the 10 healthy volunteers on 48 separate occasions. In the control periods the 24-hour urine citrate excretion varied from 75 to 850 mg/24 hours, with an average of 504 mg/24 hours. The urinary calcium excretion ranged from 18 to 443 mg/24 hours, with a mean of 114 mg/24 hours. After a single dose of 250 mg. of acetazolamide the same subjects excreted from 40 to 399 mg. in their 24 hour urine specimens, averaging 190 mg/24 hours. This fall proved to be a statistically significant alteration. The urinary calcium excretion varied from 20 to 321 mg/24 hours, with an average of 103 mg/24 hours. In each of the 10 subjects on all 24 occasions the daily urinary citrate excretion was decreased after acetazolamide. The diminution varied from 35% to 91%, with an average decline of 62±13% (S. D.). The urinary calcium excretion was not altered consistently or significantly.

When the citrate concentration of each voiding was followed in four subjects after 250 mg. of acetazolamide by mouth, the citrate excretion was found to be lowest 15 hours after administration of acetazolamide in each case. In one subject the citrate concentration had returned to normal after 22 hours, and in another, after 36 hours. In the third and fourth subjects the citrate levels were still somewhat depressed 37 hours and 80 hours after the single dose of acetazolamide.

Table 2 presents the urinary citrate excretion data obtained for the 10 patients receiving long-term acetazolamide therapy (250 mg. every 6 hours for 27 to 42 months). The citrate excretion during therapy in this group fell in the range of 6 to 75 mg/24 hours, with a mean value of 37 mg/24 hours. This is a highly significant difference from the normal output and much

TABLE 2.—*Twenty-Four-Hour Urinary Excretion of Citrate in Glaucoma Patients Taking Long-Term Acetazolamide Therapy* *

Subject	Age, Yr.	Race	Sex	Duration of Acetazolamide Therapy, Mo.	Urine Volume, Ml./24 Hr.	Citrate, Mg./24 Hr.	Calcium, Mg./24 Hr.
11 †	65	W	M	27	920	28	186
					1,300	38	198
					1,600	27	247
					960	26	183
					1,060	22	135
					1,100	32	165
12 †	68	W	M	30	1,150	41	125
					1,360	52	192
					660	42	--
13	56	W	F	38	1,000	38	--
14	68	W	F	40	2,400	23	--
15	64	W	F	42	1,900	53	--
16	39	W	F	38	1,280	29	--
17	76	W	F	36	750	75	--
18	63	W	F	27	1,950	72	--
19	71	W	F	32	970	31	--
20	60	W	F	35	450	6	--
Mean					------	37	--
Mean without subjects 11 and 12					------	41	--

* Dosage, 250 mg. every six hours.
† Symptoms of ureteral colic.

below the citrate excretion following single 250 mg. doses. It is of interest to note that the two patients (Subjects 11 and 12) who presented symptoms of ureteral colic had extremely low citrate levels in their urines but did not differ significantly from some of the eight symptom-free members of the chronic series. Furthermore, in the two patients with colic calcium excretion tended to be in the normal range.

TABLE 3.—*Urinary Excretion of Citrate in Glaucoma Clinic Patients: Comparison of Long-Term Acetazolamide Therapy Plus Miotics and Miotic Therapy Alone*

Subject	Age, Yr.	Race	Sex	Duration of Acetazolamide Therapy, Mo.	Citrate, Mg./100 Cc.	Calcium, Mg./100 Cc.
Chronic acetazolamide * and miotic therapy						
21	69	N	M	18	10	18
22	76	N	F	15	14	25
23	44	N	F	7	15	18
24	70	W	F	7	9	3
25	55	W	M	6	4	11
26	76	N	F	4	16	28
27	76	N	M	2	10	12
28	67	N	M	2	11	22
29	53	N	M	1	5	15
30	68	N	M	1	10	19
Mean				6	10	17
S. D.				--	±4	±7
Miotic therapy alone						
31	77	W	F	--	81	23
32	72	W	M	--	100	30
33	76	W	F	--	58	14
34	72	W	M	--	38	11
35	52	W	F	--	94	16
36	65	N	F	--	45	39
37	78	N	M	--	26	2
38	71	W	M	--	30	11
39	57	N	F	--	65	6
40	60	W	M	--	64	6
Mean				--	60	17
S. D.				--	±25	±12

* Dosage, 250 mg. every six hours.

In Table 3 the urinary citrate and calcium excretion in single random urine specimens obtained from 20 glaucoma clinic patients are presented. Ten of these patients had been receiving acetazolamide therapy for 1 to 18 months in addition to miotics, and the other 10 were using miotics alone. In the urine of patients receiving long-term acetazolamide therapy the citrate concentrations varied from 4 to 16 mg/100 cc., with a mean value of 10±4 mg/100 cc. (S. D.). The calcium in the urine ranged from 3 to 28 mg/100 cc., averaging 17±7 mg/100 cc. (S. D.). In the urine of patients receiving therapy other than acetazolamide the citrate concentrations fell between 26 and 100 mg/100 cc., with an average excretion of 60±25 mg/100 cc. (S. D.), and the calcium excretion varied from 2 to 39 mg/100 cc., with a mean of 17±12 mg/100 cc. (S. D.). There was thus a sharp and statistically significant differentiation of the two populations on the basis of citrate excretion. On the other hand, the average calcium excretion was approximately the same in the two groups of patients.

Comment

Following acetazolamide administration a significant depression of urinary citrate excretion without a corresponding depression of calcium excretion appears to occur uniformly in all patients tested. These findings

in man are in agreement with those reported by Harrison and Harrison [26] in rats. Gordon and Sheps [34] have observed independently a similar decrease in urinary citrate excretion after acetazolamide administration. No significant alterations in serum citrate levels were noted. The mechanism of the depressed citrate output by the kidney remains unknown. More information is needed as to the effects of acetazolamide upon citrate clearance by the kidney. The possibility exists of such induced alterations in renal citrate metabolism as are found after vitamin D administration.[35] The role of decreased citrate in the urine in the formation of renal calculi as a complication of acetazolamide therapy presents interesting opportunities for speculation and further study.

Summary

Total daily excretion of citrate and calcium was studied in 10 subjects on 24 different occasions, both without treatment and after the oral administration of 250 mg. of acetazolamide. In each patient there was a decrease in citrate output averaging 62± 13%, without a corresponding diminution in calcium excretion. The urinary output of citrate was even lower in patients on long-term (27 to 42 months) around-the-clock acetazolamide therapy (250 mg. every 6 hours), averaging 10% to 15% of normal values both on random samples and on 24-hour excretions. In two persons with recurrent ureteral colic who were taking acetazolamide, citrate excretion was markedly depressed, without corresponding decrease in the excretion of calcium. However, repeated determinations on these two patients failed to reveal significant differences in urinary citrate values as compared with the diminished citrate excretion of symptom-free glaucoma patients on similar long-term acetazolamide therapy.

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Differential Threshold Measurements on the Light Reflex of the Human Pupil

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1. Introduction

Before discussing the threshold of the pupil reflex, it seems necessary to state that its value depends mainly on intrinsic qualities of the individual nervous system and, in some degree, on the mechanical properties of the iris tissue.

We know very little about those nervous factors, but it is a fact, common to the clinician and confirmed by experiments, that some persons require a much higher energy of light to respond with a contraction of their pupils than do others, while in abnormal circumstances, as, for example, in Adie's syndrome, the insensitivity of the pupil to light stimulation is pathognomonic.

As to the iris tissue, it seems probable that the amplitude of contraction and therefore its apparent threshold is smaller in old than in young persons at any given amount of stimulation, owing to sclerotic changes in the mesodermal tissue layers of the iris.

It is evident that a quantitative knowledge about the sensitivity of the pupils might be important in the diagnosis of neurological diseases, and, under certain circumstances, we certainly would be glad to know whether the sensitivity of the pupillary system has changed after an accident or during illness, whether it is the same as measured on the left or on the right eye, and how it is distributed over the retina in cases of hemianopsia, where the absence or presence of hemiakinesia may assist in locating the lesion.

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However, before even entering these subjects, it is necessary to investigate first how variations of the stimulating light source affect the reflex threshold.

In a previous article [1] one of us (N. M. J. S.) has dealt with the absolute threshold of the light reflex. The experiments were concerned with the dark-adapted eye, to which flashes were presented, which were variable as to brightness, area, wavelength, and duration, while their distance from the fixation point could be changed as well.

Summarizing the results, we found that the threshold for the pupil reflex is mainly determined by the product of area and brightness of the stimulus source, apart from the sensitivity of the subject's pupillary mechanism. Thus, the total amount of light reaching the retina adds up to evoke the reflex, and the threshold can be reached by a small and bright source as well as by a large and dim one.

From this, it immediately follows that there exists no definite relationship between the brightness required to obtain a certain sensation of perception and the brightness required to get a contraction of the pupils. We shall explain this in some detail.

In the case of seeing, for most practical purposes, Piper's law holds; that is, the sensation is determined by the product of brightness of the source and the square root of its area.

In the case of the pupil reflex, as we stated already, the product of brightness and area is the all-important factor.

If for some person we plot the brightness required to get a just perceptible sensation against the area of a uniformly illuminated source, we will find a curve like the drawn

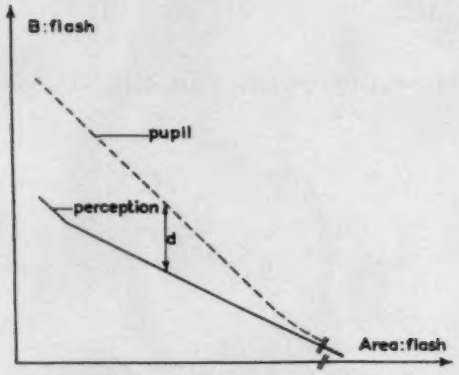

Fig. 1.—Schematic drawing, showing the brightness of a flash required so that it can be seen (drawn line) and so that it evokes a contraction of the pupils (dotted line) as a function of the area of a test field.

one in Figure 1, where the steeper slope in the left-hand part of the curve, valid only for very small areas, does not concern us now.

For small areas of a test flash, a higher brightness is required to obtain a contraction of the pupil (dotted line) than is necessary for the seeing of the light. But as the slope of this latter curve, corresponding to the formula brightness×area=constant, is steeper, it approaches the curve for seeing, and it would intersect that curve at some large area, if it finally did not bend. Indeed, if very large areas such as hemispheres are used for stimulation it appears that both curves have coincided: The same brightness which is just perceptible gives rise to a contraction of the pupil. In all instances, therefore, the light has to be perceived before it can affect the pupil. The fact that the pupil reflex, as it were, adds up all light reaching the retina is called unlimited spatial summation. In the case of perception, we speak of summation restricted to a certain area.

As to the other variables in the stimulus source, they all exert the same influence on the pupil reflex as they do on the mechanism of seeing. For both, a longer duration of the flashes presented allows for a reciprocal decrease of brightness required, up to a duration of one-tenth of a second. For longer durations the time factor becomes less important, in an identical way for both systems.

For both systems also, the wavelength of the stimulus source shows the existence of a maximum of sensitivity at about 510 mμ in the dark-adapted eye, thus showing that the rods, or at least rod-like cells, can act as active receptors, and as to the location of the stimulus on the retina, though this has not yet been investigated in full detail, it was shown that in the dark-adapted eye a relative scotoma exists for green light in the macular area for the pupil reflex as well as for perception (Arago scotoma). In the same way, the optic disc could be shown to be a blind spot for the pupil mechanism too.

To state things clearly, we should like to stress the point, as did Harms,[2] that, unless we work with light sources which are so dim as to be really at the threshold of the reflex, we do not find the blind spot, nor, by the way, do we find the central scotoma mentioned, because with brighter sources the stray light on the surrounding retina adds up to an effective level. This also explains why the blind spot, investigated by pupilloperimetric methods, shows no absolute scotoma, but a relative one only.

The measurements, summarized in the foregoing, have all been performed on the dark-adapted eye, and they concern absolute thresholds only. For two reasons it seemed worth while to extend them to the eye while it is adapted to certain colors and brightnesses. Not only did we thereby hope to get some more information on the action of the pupillomotor apparatus but, as it had appeared that the work in absolute darkness with the aid of an infrared image converter would not be compatible with clinical trials on a larger scale, we also wanted to try other methods of investigation. Though the latter problem has not yet been solved in detail, the present data open the way to an interpretation of reflex data obtained by direct visualization of the pupil.

2. Investigations on the Differential Threshold of the Pupil Reflex

Methods.—In the determination of a differential threshold, the retina, or a part of it, is, by definition, adapted to a certain brightness, which will be called B.

On this adaption field a test spot is superimposed, the brightness of which we call ΔB. The brightness of the test spot at the threshold of perception is called $\Delta B_{perc.}$, and if the test spot is just bright enough to give rise to a contraction of the pupils, its brightness is noted as ΔB_{pupil}.

In all these experiments we worked with the aid of an artificial pupil, through which the test light and the light from the adaptation source reach the eye. Otherwise the pupil, screening off part of the light which falls on the eye, would show oscillations caused by its regulating the amount of light which falls on the retina. With an artificial pupil, however, no pupillary unrest can be noted.

The Apparatus: Through an artificial pupil (1 mm. in diameter) the subject looked with his right eye at a fixation light, and at the same time he was aware of an illuminated circular background, the diameter of which was always 8 degrees (except in the experiments described in Part III). The fixation light could be superimposed on the center of the background, and in that case it had the form of a cross, the center of which was dark, so that the foveal functions could be investigated. In other instances and in most of the experiments reported here, the fixation light, one dim point source, was presented 9 degrees nasal to the center of the background, so that a distance of 5 degrees existed between this light and the border of the background. On the center of this background, the brightness and color of which were variable, a test spot could be superimposed.

The duration of the test flash was one-tenth second, and its frequency, once in every three seconds. Its diameter could be varied between ¼ and 8 degrees; in the latter case it covered the background of 8 degrees entirely.

The brightness of the background and of the test flash could be varied separately and quantitatively by controlling the current through two ribbon filament lamps. By means of Planck's tables and the calibration reports of the lamps, their relative emission at any wavelength can be calculated. Calibrated neutral filters were used to extend the range of brightness. The slits of a double monochromator determined the wavelengths of background and flash.

A dimly illuminated white cardboard ring at a suitable location assisted in keeping the optical axis of the eye in alignment with the axis of the illuminating system, thus preventing errors in the measurements due to the Stiles-Crawford effect. The pupil reflex was observed on the left eye.

We called the threshold for perception ($\Delta B_{perc.}$) the brightness of the test flash which could be perceived in 60% of the cases in which it was presented. Similarly, the threshold for the pupil reflex (ΔB_{pupil}) was determined by observing through an infrared image converter the number of contractions of the pupil at different brightnesses of the flash. The threshold was reached at the brightness where 60% of the flashes resulted in a contraction.

In fact, we always observed the pupil of the nonstimulated (left) eye, as the other one was hidden by the screen with the stenopeic hole, which served as an artificial pupil.

Therefore the consensual reflex was measured rather than the direct one, but the investigations of Loewenstein, showing the similarity of the two reflexes as to speed and amplitude, seem to justify this procedure.

Though the use of an image converter is probably the most delicate method in obtaining thresholds for the pupil reflex, it requires many adjustments of the observing system and therefore it is rather time-consuming. Also, the observer gets tired very soon.

That is the reason why we tried another procedure, based on the old principle of the entoptic image of the pupil.

If a point source of light is placed at a short distance before the cornea, well within the near point of the eye, a circular patch of light will be projected on the retina, the diameter of which is determined by the diameter of the pupil. This method is easy to demonstrate if one looks through a pinhole in a piece of paper at the sky, covering and uncovering the other eye and thus making the pupils move.

If we wanted to use this method, two preliminary investigations had to be performed.

1. It had to be established whether a steady illumination of the eye, observing its own pupil, changed the threshold of the pupil reaction in the other eye.

This appeared not to be the case, even if an extremely bright light directed into one eye contracted both pupils continuously to 3.5 mm. (adapting field 20 degrees, 200,000 times brighter than its own absolute threshold). It is a remarkable fact that the sensitivity of the reflex seems not to be affected by the state of adaptation and stimulus conditions of the other eye or the diameter of the pupils. We have extended these measurements by presenting to the left eye a large and very bright field in which a pair of cross wires were exposed. (This was done, making use of a Maxwellian view, in such a way that contractions of the left pupil could not interfere with the brightness of the field presented.)

These could be brought to fusion with a similar pair of cross wires in the center of the variable background.

The differential thresholds thus obtained for perception and for the pupil reflex appeared not to be affected to any appreciable degree by the brightness of the field presented to the left eye.

2. The entoptic method had to be compared with the method of direct observation through the infrared converter.

Comparative measurements, done with both methods, showed a substantial agreement of results. In a large part of the measurements we therefore abandoned the infrared converter in favor of the entoptic observation of the pupil.

We made use of two small holes, separated by 2 mm. and placed at about 2 cm. from the cornea. Both were dimly illuminated. In this way small contractions of the pupil can be observed with greater ease.

All the results given in this article have been obtained on the eyes of one of us (M. A. B.), though the general shape of almost every curve has been checked on other subjects as well.

Results.—I. The Law of Reciprocity of Brightness and Area of the Test Flash with Regard to the Pupil: The law of reciprocity

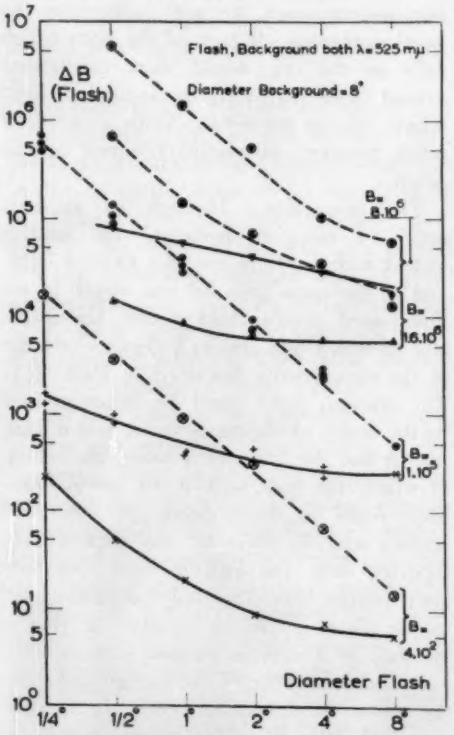

Fig. 2.—$\Delta B_{pere.}$ (drawn lines) and ΔB_{pupil} (dotted lines) as a function of the diameter of a green test flash for four different brightness levels of a green background. At each background brightness different symbols are used, simple ones for the $\Delta B_{pere.}$ values (linked by drawn lines) and encircled ones for ΔB_{pupil} (linked by dotted lines). $B=4.10^5$ corresponds to a background brightness 400 times its own threshold of perception. Presentation on the retina was 9 degrees nasal to the fovea.

of brightness and area of the test flash with regard to the pupil reflex has been verified in the four possible combinations of red (λ=650 mμ) and green (λ=525 mμ) flashes on red and green backgrounds of variable brightness.

Figures 2 and 3 present the data obtained for green flashes on a green background and for red flashes on a green background, respectively. The presentation on the retina was 9 degrees nasal to the fovea.

From these Figures it will be seen that the values for ΔB_{pupil} all lay on straight lines, corresponding to the following formula:

$\Delta B_{pupil} \times$ area of test flash $= C$

The values for $\Delta B_{perc.}$, on the other hand, lay on rather complex curves, the course of which is affected by the background brightness.

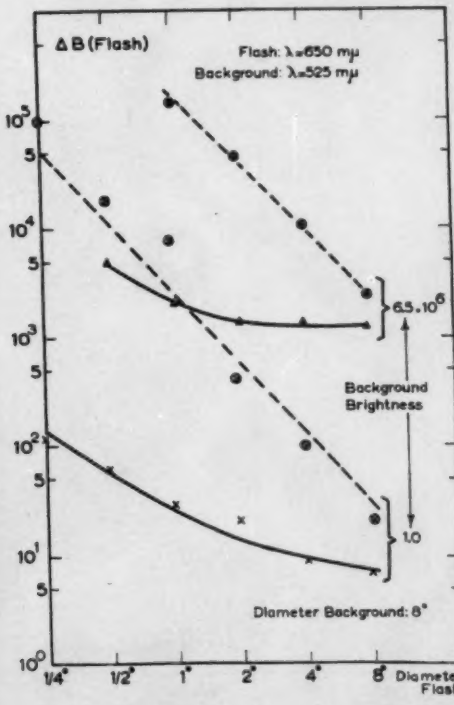

Fig. 3.—$\Delta B_{perc.}$ and B_{pupil} for a red flash on a green background for two different brightness levels of the background, which was just perceptible (B=1.0) in the lower set of curves and 6.5×10^6 times above its own threshold in the upper one. Drawn lines and symbols stand for $\Delta B_{perc.}$. Dotted lines and encircled symbols stand for ΔB_{pupil}. Presentation on the retina was 9 degrees nasal to the fovea.

Furthermore, it may be remarked that at any diameter of the test spot the fraction $\frac{\Delta B_{pupil}}{\Delta B_{perc.}}$ is a constant, regardless of the background brightness.

Similar results were obtained in other experiments, where red flashes were used on green and red backgrounds.

Some discrepancy of the general law could be observed only in those instances where the background brightness was very high, as is seen in the two upper sets of curves of Figure 2. There, the slope of the ΔB_{pupil} curve tends to level off for areas of the test spot larger than 4 degrees, and the same phenomenon may be expected to happen for smaller background brightnesses and larger areas of the test spot than we have actually used. Evidently, the ratio $\frac{\Delta B_{pupil}}{\Delta B_{perc.}}$ cannot fall below a certain value, or, stated otherwise, the discrimination value $\Delta B_{perc.}$ has always to be exceeded by a minimal amount before it evokes a contraction of the pupils.

This behavior may be compared with that of the absolute threshold of the pupil reflex, mentioned in the introduction, where we said that the threshold for the pupil reflex always exceeds the threshold of visibility, so that a pupil contraction never occurs without the flash having been perceived.

The results obtained by presenting red flashes on a red background or by presenting green flashes on a red background are not given in detail, as they are identical to those of Figures 2 and 3.

The relationship between area of test spot and background brightness has also been investigated for the foveal region.

In this instance, the situation is somewhat more complicated, as, with increasing areas of the test spot, regions of different retinal sensitivity are stimulated, especially so if green test flashes are used.

The irregular curves obtained in that way are shown in Figure 4, where the results are plotted for a green test flash on a dark background. The increase of sensitivity of

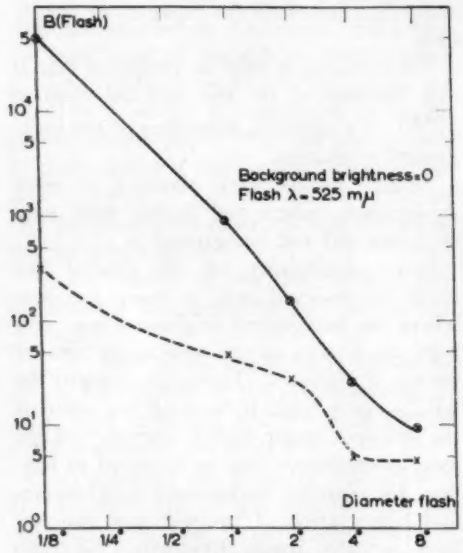

Fig. 4.—B_{pupil} (drawn line) and $B_{perc.}$ (dotted line) as a function of the diameter of a green test flash; absolute thresholds. Foveal presentation.

the visual system at diameters of the test spot between 2 and 4 degrees is very great; that of the pupillary system seems less dramatic, and it begins at smaller areas, but no conclusions can be drawn from these data, as we do not know how the curve for the pupil reflex is affected by the nearness of the curve for perception.

II. The Ratio Between Visual and Pupil Reflex Thresholds with Increasing Background Brightness: In the following paragraph we shall see how the pupil reflex threshold and the visual threshold depend on the brightness of the background.

The same combinations of red and green flashes on red and green backgrounds as mentioned previously were used in this series of experiments.

(*a*) Green flashes on a green background. The results are given in Figure 5.

The parallelism between the corresponding curves for the reflex and for perception is evident, and we therefore are allowed to conclude that the pupil reflex threshold is affected here in the same way as is the threshold for perception.

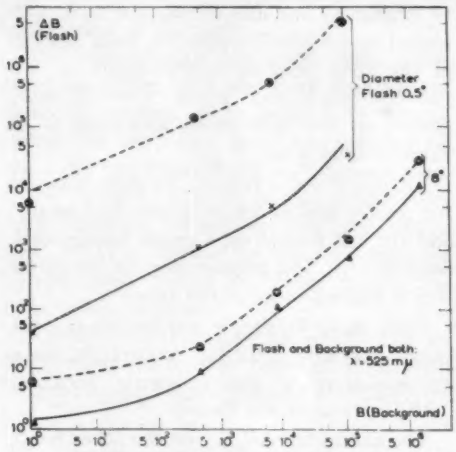

Fig. 5.—The variation of $\Delta B_{perc.}$ (drawn lines) and ΔB_{pupil} (dotted lines) with increasing background brightness, B, for green test flashes on a green background. Diameters of test field were 0.5 and 8 degrees. $B=10^p$ stands for just perceptible brightness of the background. Presentation was 9 degrees nasal to the fovea.

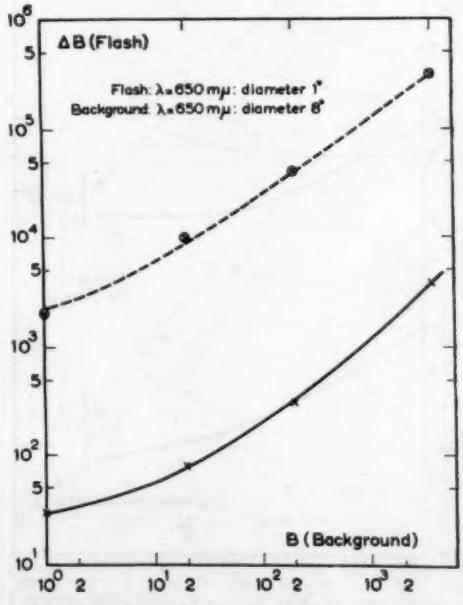

Fig. 6.—The variation of $\Delta B_{perc.}$ (drawn line) and ΔB_{pupil} (dotted line) with increasing background brightness, B, for red flashes on a red background. Diameter of test field, 1 degree. $B=10^p$ stands for just perceptible brightness of the background. The ratio $\frac{\Delta B_{pupil}}{\Delta B_{perc.}}$—actually was 100 instead of 10, as shown here. Presentation was 9 degrees nasal to the fovea.

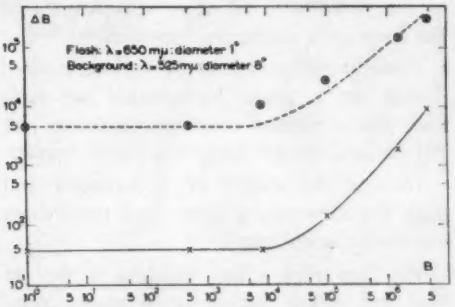

Fig. 7.—The variation of $\Delta B_{pere.}$ (drawn line) and ΔB_{pupil} (dotted line) as a function of the background brightness, B, for red flashes on a green background. Diameter of test field, 1 degree. $B=10^0$ stands for just perceptible brightness of the background. Presentation was 9 degrees nasal to the fovea.

(*b*) In Figure 6 similar results are given for the case that red flashes are used on a red background. Again we find a parallelism between pupil reflex curve and that for perception, while the slope of both curves corresponds to that given in Figure 5 for green flashes on green backgrounds.

In the following Figures we will see what happens if the color of the test field and that of the background are not identical.

(*c*) The first combination is that where red flashes are used on a green background (Fig. 7). Here the effect of the brightness of the background on the respective thresholds is very small indeed. It appears only after the background brightness has been increased about 7000 times above its own threshold.

Bouman [3] has discussed in detail this phenomenon and others, concerning the same, though smaller, types of stimuli and background.

As to the behavior of the pupil reflex, however, it appears that here again the curves for $\Delta B_{pere.}$ and ΔB_{pupil} run practically parallel, though there is a slight tendency toward convergence at high brightness levels of the background.

(*d*) This convergence becomes more evident if we use the last of our four possible combinations, i. e., a green flash on a red background. This can be seen from Figure

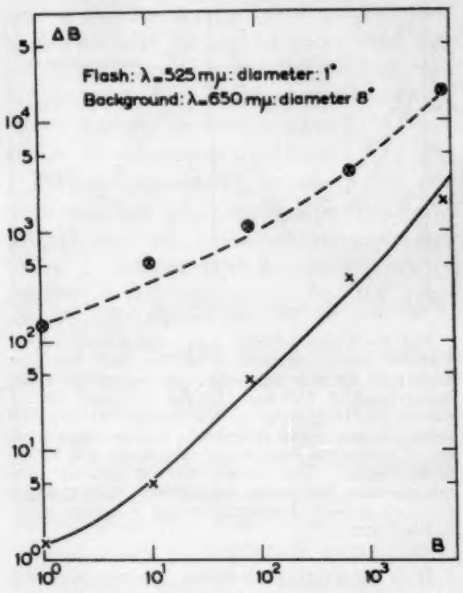

Fig. 8.—The variation of $\Delta B_{pere.}$ (drawn line) and ΔB_{pupil} (dotted line) as a function of the background brightness for green flashes on a red background. $B=10^0$ stands for just perceptible brightness of the background. Presentation was 9 degrees nasal to the fovea.

8. Here the ratio $\frac{\Delta B_{pupil}}{\Delta B_{pere.}}$ decreases from 100 at the lowest background brightness to about 7 for the highest one.

In comparing this set of curves with the one in Figure 6, for the same red flashes on a red background, we see that the general slope of the pupil threshold curve is the same in both instances, while the curve for the threshold of perception has changed its slope; it is much steeper in Figure 8.

We can say that if green flashes are presented on a red background the pupil reflex becomes relatively more sensitive than the visual function as the background brightness increases.

It is likely that this effect is due not so much to a change in the characteristics of the pupil mechanism as to some factor which depresses the ability of seeing, so that the visual threshold curve is forced to a steeper slope than otherwise would be the case, for example, with a green background or a low-intensity red one.

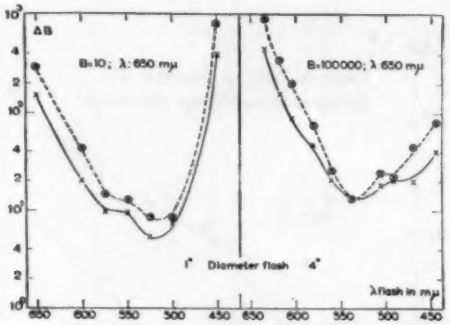

Fig. 9.—Visual (drawn lines) and pupillomotoric (dotted lines) sensitivity of the eye for test flashes of varying wavelength presented on a red background, λ 650 mμ. In the left-hand set of curves the brightness of the background was 10 times its own visual threshold; for the right-hand set of curves the background brightness was 10,000 times higher. The values on the ordinate are relative ones, the curves having been shifted along this axis at will. Presentation was 9 degrees nasal to the fovea.

It is interesting to know the relationship between the wavelength of background and flash at which this phenomenon of convergence occurs in the most striking way.

We investigated this for a red background only, using two different brightness levels, and varied the wavelength of the flash. The results are shown in Figure 9. In the left-hand set of curves the brightness of the background was only 10 times its own threshold of perception, and it is seen that in this instance the curves for the threshold of perception and for the threshold of the pupil reflex (the latter having been shifted downward to make comparison easier) run parallel.

In the right-hand set, the brightness of the red background has been increased to 10^6 times its own visual threshold, and now parallelism between the two curves is lost, their mutual distance being largest towards both ends of the spectrum, while somewhere about 540 mμ they come nearest to each other (in this Figure the curves have been made to touch each other for the sake of comparison).

This means that when a 540 mμ flash is used on a 650 mμ background of high intensity the pupil reflex is most sensitive as compared with all other wavelengths of the flash on a similar background.

From the experiments of various colored flashes on a green background we have seen that a similar convergence occurs for red flashes, though here it is much smaller.

In case the colors of background and flash are identical, a most rigid parallelism has always been found.

We then tried yellow and blue flashes on blue and yellow backgrounds, respectively, investigating whether the pupil reflex became more sensitive than perception with increasing brightness of the background. In all these instances a straight parallelism between the two functions was found as the brightness of the background increased.

It therefore seems justified to summarize that the convergence effect, by which we understand the phenomenon that the ratio between the brightness of a flash of given size at the pupil reflex threshold and at the threshold of perception ($\Delta B_{pupil}/\Delta B_{perc.}$), decreases with increasing brightness of the background and does occur only if green and red flashes are superimposed on red and green backgrounds, respectively, while it is probably most apparent if a green test flash of about 540 mμ wavelength is presented on a red background.

III. The Ratio Between Brightness Content of the Test Flash and the Energy Content of the Background: Using a test flash of a constant size and a background of a constant brightness, we can determine the brightness of the test flash required to give rise to perception and to a contraction of the pupils, respectively, as a function of the area of the background.

The possible combinations have not yet been investigated in detail. In Figure 10, however, it can be seen what happens if a green flash is presented on a green background, the size of the latter being increased from 0 to 8 degrees.

From this and the foregoing experiments the general principle can be deduced with a fair security.

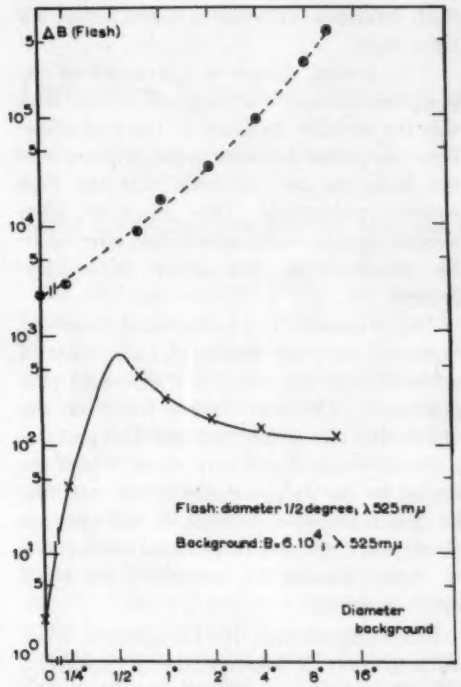

Fig. 10.—The brightness of a test flash, green, 0.5 degree in diameter, required for the visual threshold (drawn line) and the threshold of the pupil reflex (dotted line) as a function of the area of a green background, on which it was superimposed.

As the size of the background increases the intensity of the flash has to be increased also. For the largest backgrounds a ratio of 1:1 seems to exist between the increments of the two factors, but for the smaller-sized backgrounds the energy of the test flash rises more slowly than that of the background, the ratio being in the order of 1:0.4, or, stating this differently, we can say that the coefficient, k, giving the slope of the curve for large backgrounds probably is 1, but for the smaller backgrounds we find that $k=0.65$.

This is in strong contrast to what happens with the visibility curve: Here the general tendency is that with increasing area of the background the energy of the flash required so that it can be perceived decreases slowly. It is, however, extremely low if no background is present at all and very difficult to determine if the size of background and test flash coincide, so that no contours can be perceived. The slow descent of the curve which follows thereon is caused by such effects as decreasing irradiation.

Further experiments, in which the test flash was not superimposed on the background but was presented some degrees above it, showed that the results can be compared with the curve for the pupil reflex given in Figure 10.

Here also there exists a definite relationship between the size of the background and the energy content of the test flash. This fact implies the possibilities of investigating the effect of light flashes on the sensory mechanism of the eye, while circumventing the complications which arise from local adaptation and varying spatial summation.

3. Comment

From the foregoing experiments, notably those presented in Parts I and II, where a background of constant area was used, we can answer the question of whether a light flash of certain intensity and area can evoke the pupil reflex.

If only the energy content of the flash is high enough in relation to the brightness of the background, the latter being kept at constant size, the pupil will contract. That is, $\Delta E_{\text{flash}}/B_{\text{background}}=C$, where C is a constant related to the sensitivity of the individual pupillary system and the mechanism of perception.

From what is known about the effects of changing the area of the background (See Part III) it seems justifiable to put this formula in a more general way:

$$\Delta E_{\text{flash}}/E_{\text{background}}=C.$$

Several exceptions, however, as to this general statement exist.

Some of them are caused by the fact that the red- and the green-sensitive systems of the eye sometimes act independently of each other. This, for example, is the case in the combination of red flashes on a green background (Fig. 7): For a considerable range

of increasing brightness levels of the background the thresholds for both the pupil and perception are not affected by the brightness of the background at all.

Other deviations of the general law are due to the fact that the pupillary mechanism cannot be excited unless the test flash has been perceived. This can be seen from the curves in Figures 2 and 3 and the drawing in Figure 1: For large test flashes the law of reciprocity of area and brightness, which is the same as that of equal energy content, expressed above, cannot hold.

The phenomenon of convergence, mentioned in Part II (*d*) and shown in Figure 8, is an exception which is somewhat more difficult to explain. With the assumption that the green-sensitive system (rods) interacts over much larger areas than the red one (cones),[4] a response of the former could readily be suppressed by the latter system as it becomes more saturated. This would become apparent in a relative increase of the visual threshold with increasing brightness of the background.

Independent of this kind of interaction, the mechanism which serves the pupil reflex shows a much simpler behavior, according to the law of energy content which governs the light reflex of the pupil.

Use of auto-observation made it possible to pass by the infrared image converter, while, on the other hand, the finding that the pupil reflex threshold in one eye is independent of the state of adaptation of the other eye offers a way of investigating the reflex threshold in other persons by a simpler method than those used until now. Some practical difficulties, inherent in direct hetero-observation, have been solved theoretically at least. They will be discussed in another paper.

4. Summary

Unlike the laws which govern the threshold of perception, those which underlie the light-reflex system of the pupil can be summarized by stating that, with constant backgrounds, only the energy content of a light flash determines whether a reflex action will take place.

This is first shown in a number of experiments where the area of a test flash was the variable. Increase of the area allows for a reciprocal decrease in the brightness of the flash, on the condition that the flash remains perceptible. This effect of unrestricted spatial summation is not affected by the simultaneous presentation of a background.

The presence of a background, however, raises the pupillary threshold, an increase of its brightness increasing the threshold proportionally. This was verified for green and red flashes on green and red backgrounds and vice versa. Some exceptions, which are caused by the independence of the red- and the green-sensitive systems in the eye, are discussed. It appears that mutual interactions of these systems do not affect the pupil reflex threshold.

Increasing the area of a background, while its brightness is kept constant, requires a proportional increase of the brightness of the test flash, at least for large backgrounds.

Therefore, we conclude that the energy content of the flash in relation to that of the background determines whether a contraction of the pupils will take place.

Dr. Jac. P. Thijsselaan 23.

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Cataract Wound Healing in the Rabbit Eye

An Experimental Evaluation of the Effects of Antihistamines on Corneal Wound Healing

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In the past several years, the role of histamine as the culprit accountable for the discomforts of inflammatory processes in general has been brought to light. There is an awareness of the association of anaphylactic and allergic reactions with histamine. It has been shown also that histamine, a product of the amino acid histadine, which is present in all complete protein, is released from tissue cells in many abnormal states, particularly trauma. There is, however, as yet, no definitely proven function of histamine in normal physiological states.[1] It is known that histamine causes a vasodilatation of the arterioles and capillaries, and with sufficient histamine release the permeability of the vessels is altered. The result is a transudation of plasma, protein, and fluid into the extracellular spaces, producing edema and inflammatory exudate about the blood vessels.[2] The triple response of Lewis is a good example of local histamine release. This theory postulates that traumatic shock is the result of toxemia caused by release of histamine or histamine-like substances from the injured regions. It is believed that histamine is present in an inactive form in most tissue cells of the body and that it becomes effective only after damage or irritation of the cells.

In 1955, in the *Journal of Oral Surgery*[3] there was a report of seven patients who had oral surgery and in whom studies of saliva were made for histamine content before and after surgery. The histamine content was seen to rise from an average of 169μg. per liter before surgery to an average of 668μg. per liter after surgery. The same procedures were performed in another seven patients with use of an antihistamine pre- and postoperatively. This time, the histamine showed a rise from an average of 168μg. per liter to an average of only 261μg. per liter.

On the basis of the fact that histamine is released during surgical trauma, it was decided to determine whether the edema and inflammation promoted by histamine delays wound healing. In fact, in the past few years, there have been several reports, both clinical and experimental, of increased wound healing with the use of antihistamines.

In 1951,[4] in a series of 100 cases of accidental trauma in which antihistaminic therapy was used as compared with another series of 100 cases in which it was not used, the observation was made that pain and edema were markedly decreased as was the general tissue reaction.

In 1952, Silverman[5] reported that the antihistamines greatly improved the postoperative course following oral surgery. He stated that the great proportion of wounds healed by primary intention and that secondary hemorrhage as a complication of surgery was not seen during the use of these drugs. Slough as a complication was virtually eliminated, and there was a great decrease in the incidence of swelling.

In an experiment with a group of guinea pigs,[6] a standardized flank wound was inflicted on the animals and the rate of healing

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was measured daily and recorded. Two weeks later the same animals were wounded on the opposite flank, but this time antihistamines were used pre- and postoperatively. In the control group the average time for complete healing was 11.3 days, with a mean of 50% healing of 8.22 days. With the use of antihistamines, in the second group, the average number of days for complete healing was found to be 8.5, or 2.8 days less than the control group, and the 50% mean was 5.21 days, as compared with 8.22 days in the control group.

In view of these experimental findings and the clinical observations we decided to determine the effect of antihistamines on the healing of the cataract wound. I might add, at this point, that the antihistamines do not work by destroying histamine but in some manner absorb onto the cells and by an as yet undetermined mechanism prevent histamine from affecting cells in the usual manner.

Our experiment consisted of making a corneolimbal section in rabbits with a keratome and enlarging the section with Westcott scissors to 8 mm. in length. We then irrigated the anterior chamber with sodium citrate, as there is an excess of fibrin in the rabbit aqueous and we did not want this to clot in the wound. A 000000 black nonabsorbable surgical (silk) corneoscleral suture was placed at either end of the incision to appose the wound edges. The lids were then closed with silk mattress suture. The eyes were enucleated at intervals varying from 1 to 14 days postoperatively.

Approximately three weeks later, the opposite eye of each rabbit was operated upon in the same manner, with use of procaine crystalline penicillin G, 300,000 units intramuscularly pre- and postoperatively, as had been used in the first group. In addition, Pyronil * a long-acting injectable antihistamine, was given daily, pre- and postoperatively, in the dosage of 10 mg. per kilogram, which is eight times that of the adult human dose in proportion to the body weight. Once again, the eyes were enucleated from 1 to 14 days postoperatively. The rabbit which had its eye enucleated on the first postoperative day in the control group had its fellow-eye enucleated on the first postoperative day in the second group, and so on. In this way, we hoped to compare histologically two eyes from the same animal which had had the same operative procedure and medication except for the addition of the antihistamine.

Technically, the procedure is difficult on rabbits, for there is a great tendency of the iris to prolapse and an iridectomy cannot easily be performed because of the tremendous hemorrhage induced. We first tried to test wounds by forcing them apart. We did this by inserting a 27-gauge needle at the limbus into the anterior chamber and injecting air into the chamber via this needle, which was connected to a mercury manometer so as to measure the pressure at which the wound might burst. However, in many cases we were unable to force the wound apart, even at a pressure of 300 mm.Hg, and had to abandon this method.

We should like to comment on the clinical appearance of the two sets of eyes: In the control group the amount of reaction observed was minimal, with no evidence of frank prolapse. There was no discernible gross infection, and the tissue reactions appeared minimal as well, despite the fact that the rabbits were extremely active and pugnacious toward each other. In no case did the corneoscleral suture slough out. In the second series, despite the fact that the rabbits were very sedated, owing to the antihistamine, we had one case of frank prolapse and three cases in which the black silk sutures had sloughed out, namely, in the eyes which were enucleated on the 10th, 12th, and 14th postoperative days. In addition, there were several cases of frank infection, with hypopyon present in two.

Histological examination, the photomicrographs of which are pictured here (Figs. 1-16), indicates that healing in the control

* Pyronil was supplied by Eli Lilly and Company.

Fig. 1.—Rabbit 572, control group, two days after operation, O. D.; × 35. In this section, note that the epithelium has already bridged the wound. There is already an attempt at healing of the wound edges.

Fig. 2.—Rabbit 572, antihistamine group, 2 days after operation, O. S.; × 35. It will be noted here that gaping of the wound still persists. There is no attempt at healing as yet.

Fig. 3.—Higher power view (× 100) of Figure 1, of the control group. This readily shows the epithelium bridging the wound defect, the inflammatory cells in and about the wound, and the early attempt at fibrous union.

Fig. 4.—High-power view (× 100) of Figure 2, antihistamine group. It is noted here that there is marked gaping of the wound and no attempt at wound healing, as well as little evidence of inflammatory reaction.

Fig. 5.—Rabbit 533, control group, five days after operation, O. D.; × 35. Healing has advanced well here. The area of the wound is densely fibrosed. The iris is adherent here, as in most of the sections shown.

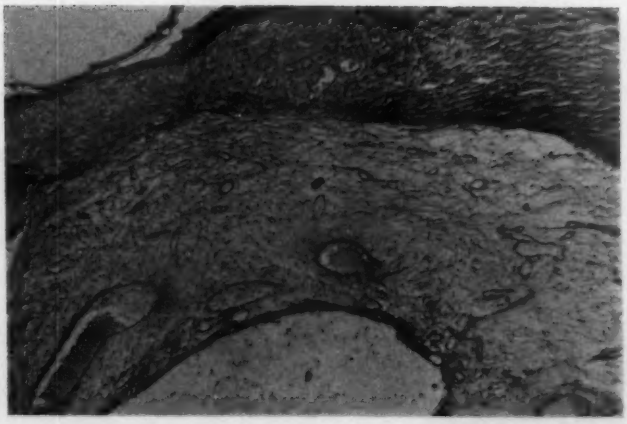

Fig. 6.—Rabbit 533, antihistamine group, five days after operation, O. S.; × 35. Once again, the adherent iris is present. However, there is considerable separation of the lower edge of the wound, as represented in the upper right hand part of the picture, where a cut scleral edge is seen. Fibrosis is not as advanced as in Figure 5.

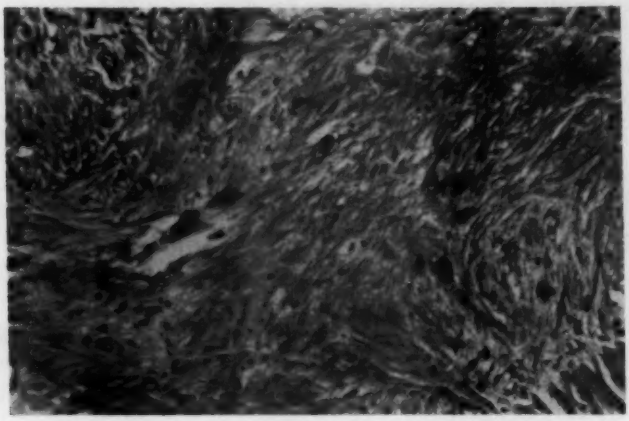

Fig. 7.—High-power view of Figure 5 (× 100), control group, five days after operation. Note here the density of the tissue filling in the wound defect.

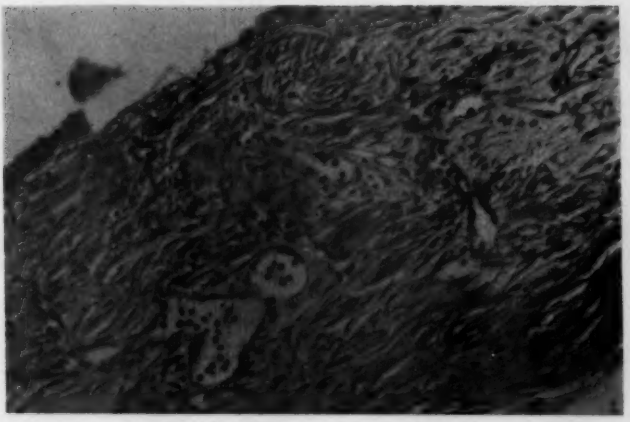

Fig. 8.—High-power view of Figure 6 (× 100), antihistamine group, five days after operation. The wound here shows more loosely packed fibrous tissue, with healing not as advanced as in Figure 7.

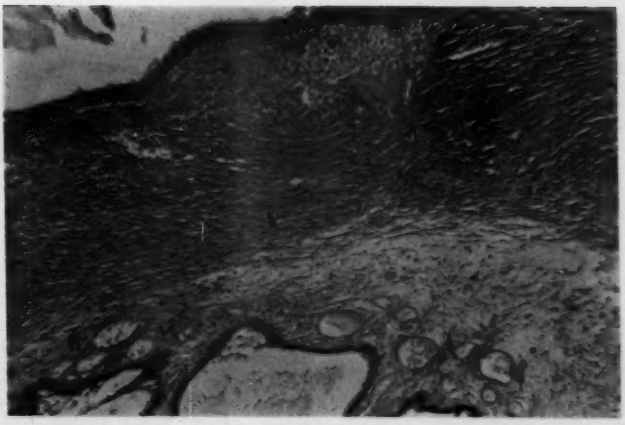

Fig. 9.—Rabbit 987, control group, 10 days after operation, O. D.; × 35. Healing very advanced at this stage.

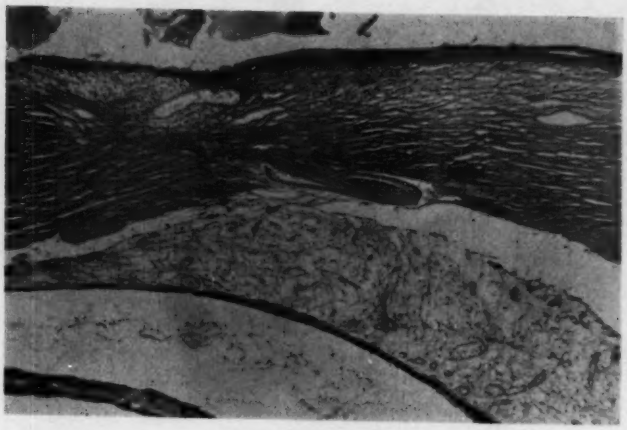

Fig. 10.—Rabbit 987, antihistamine group, 10 days after operation, O. S.; × 35. In comparison with Figure 9, the rate of healing is not as advanced. Vacuolation is present. Fibrosis is not as evident.

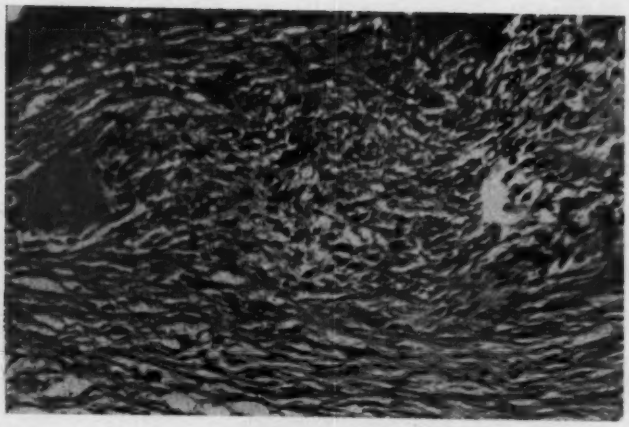

Fig. 11.—High-power view of Figure 9 (× 100), control group, 10 days after operation.

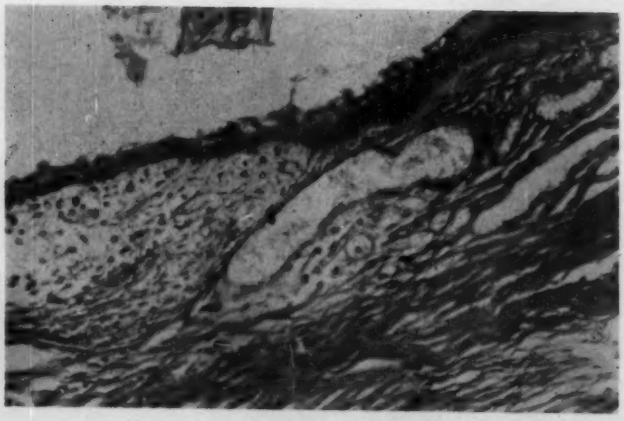

Fig. 12.—High-power view of Figure 10 (× 100), antihistamine group, 10 days after operation. In comparison with Figure 11, it is readily apparent that healing has progressed further in the control group.

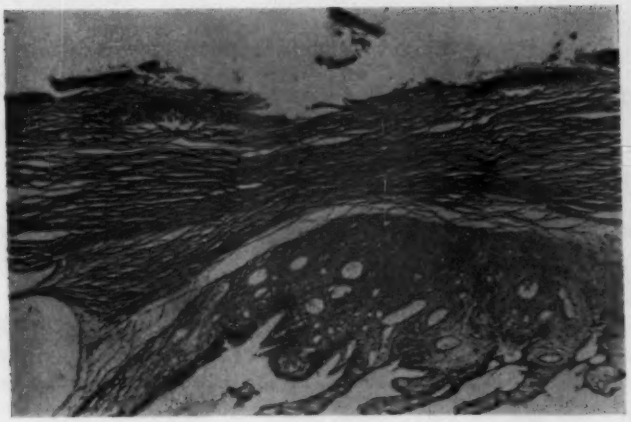

Fig. 13.—Rabbit 517, control group, 14 days after operation, O. D.; × 35. Here the fibrillar structure of the wound area has been reestablished. The only evidence of the site of the wound is the curled edge of Descemet's membrane present at the extreme right and left side of the photograph, just above the iris and ciliary body.

Fig. 14.—Rabbit 517, antihistamine group, 14 days after operation, O. S.; × 35. Fibrosis is occurring. There is still extravasation of blood in the tissue. This more closely represents the healing as in Figure 5, control group, five days after operation.

Fig. 15.—High-power view of Figure 13 (× 100), control group, 14 days after operation. This shows the normal structure of the corneal scleral fibers in the region of the wound.

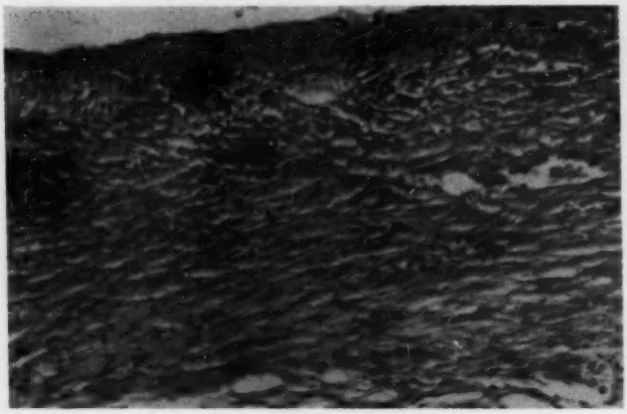

Fig. 16.—High-power view of Figure 14 (× 100), antihistamine group, 14 days after operation. There is still an inflammatory reaction. This section should be compared with Figure 7.

series is equal to or slightly better than or more advanced than healing in the antihistamine-treated group, but in no case was healing observed to be more advanced in the antihistamine-treated group.

Perhaps an explanation for our results of delayed wound healing in the antihistamine-treated group may be found in the fact that wounds will not heal without an inflammatory response of some sort. Without inflammation there cannot be the sequence of events which leads to the formation of granulation tissue. Antihistamines may depress the normal inflammatory response which is necessary for adequate wound healing in much the same way as the steroids suppress the inflammatory response and thus delay wound healing.

In summary, then, although in oral surgery the antihistamines have been credited with promoting wound healing and diminishing tissue reaction, it has been found that, in the rabbit eye, corneal wound healing and tissue reaction are adversely affected by antihistamines.

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Studies in Experimental Ocular Tuberculosis

XVIII. The Effect of Cortisone Combined with Specific Antibacterial Therapy on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit

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From 1948 to 1954 a series of papers on the effect of various antibacterial agents on experimental ocular tuberculosis appeared from the Wilmer Institute. These various studies have indicated that streptomycin is the one antibiotic thus far discovered with a strong antibacterial action against Mycobacterium tuberculosis. A number of the synthetics—glucosulfone (Promin), thiazosulfone (Promizole), aminosalicylic acid, and isoniazid—also have a specific antibacterial effect on the bacillus. This varies from a moderate bacteriostatic up to an actual bactericidal effect. It was further shown in these experimental studies that when streptomycin is used in combination with one of the synthetics as an adjuvant the antibacterial and therapeutic result is much greater than would be expected by a mere additive effect. It suggested a synergetic action of the two therapeutic agents. It was also shown that the use of these agents in combination inhibited to a considerable extent the development of bacterial resistance. Other similar investigations from various laboratories have fully confirmed these observations.

In 1952 experiments were reported in which the action of corticotropin and the corticosteroids on experimental ocular tuberculosis in normal and immune-allergic rabbits was explored.[4] In these experiments the rabbits were pretreated with either corticotropin or the corticosteroids for four to eight days prior to inoculation of tubercle bacilli into the eyes. In the normal rabbits the resultant ocular tuberculosis followed the usual rapid and fulminating course which is constantly observed in the nonimmune rabbit, and no difference in the intensity of the disease in the treated rabbits and untreated controls was noted. In the absence of a systemic immunity these hormones certainly had no deterrent effect on the progress of the disease. In the immune-allergic rabbits there was a marked difference in the results in the rabbits receiving hormonal therapy and in those which were left untreated. These animals received either corticotropin systemically or cortisone systemically or topically. They were pretreated for four days prior to inoculation of tubercle bacilli into the eyes. Treatment thereafter was continued for approximately two months. The effect of the administration of these hormones on the pattern of the resultant ocular tuberculosis was the same with corticotropin systemically or cortisone systemically or topically. The focal reaction to the tuberculin in the inoculum was suppressed, and the outbreak of objective ocular symptomatology was delayed for a 30- to 50-day period, during which time the eyes of the treated rabbits remained intact and free of clinical evidences of tuberculosis. At the end of this period, however, the rabbits began to develop both ocular inflammation and tuberculous lesions in the eyes which had had inoculations. The first organic changes observed were showers of soft tubercles on the iris. Histological examination of an eye from a rabbit killed at this time showed so-called "soft" tubercles on the surface of the iris. Acid-fast stains showed innumerable tubercle bacilli both in the stroma of the iris and in the extratissue exudates. Apparently

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during the period of quiescence, the bacilli had multiplied to such an extent that the anti-inflammatory action of the hormones was no longer adequate to combat the tissue response to such a massive bacterial insult. When treatment with hormones was stopped the ocular disease progressed rapidly, with secondary glaucoma, buphthalmos, and finally rupture of the globe. In short, the restrained self-limited disease shown by the untreated control immune-allergic rabbits was transformed into a malignant, fulminating destructive disease of the type seen in the nonimmune animal. Further observation of these treated immune-allergic rabbits suggested that this transformation of the clinical picture was not due to any depression in the acquired immunity but was probably related to the inhibition of the inflammatory reaction by the steroid therapy. In the suppression of this inflammatory reaction, there was a concomitant suppression of the mobilization of the mononuclear phagocytes and an inhibition of the fibroblastic reaction—Nature's first line of defense against a tuberculous infection was put out of action.

Subsequent clinical observation has confirmed the danger of using hormonal therapy in ocular tuberculosis. Several cases of ocular tuberculosis have been seen in which, although the early energetic steroid therapy was followed by a circumscription of the lesions and what was apparently a marked subjective and objective improvement, when treatment was terminated, or even during the continued administration of the steroids, there were sharp recurrences of the uveitis. These were almost invariably of increased intensity, and in some of these patients vision was permanently destroyed.

It has now been suggested that a combination of corticosteroid therapy with specific antibacterial therapy may be the most effective manner of treating some forms of tuberculosis. Thus, Benhamou and Timsit[5] report four cases of tuberculous meningitis successfully treated with a combination of antibacterial therapy and intraspinal injections of hydrocortisone. Various other reports likewise indicate that the combination of antibacterial and adrenal corticosteroid therapy is beneficial in the treatment of tuberculous meningitis. Quite recently, Cooke,[6] in reporting on the successful treatment of tuberculous meningitis, sums up the situation on the use of the corticosteroids as follows: "The theory behind the use of Cortisone is to decrease the allergic response to tuberculin, thereby limiting the amount of fibrous reaction in the central nervous system, which eventuallly causes a block in the flow of cerebrospinal fluid with resultant hydrocephalus. Autopsies in the cases of many survivors, who die late, show that the tuberculous infection is overcome, death being due to cerebrospinal fluid block and the residual inflammatory reaction."

In the treatment of pulmonary tuberculosis reports vary regarding the desirability of using steroids in conjunction with specific antibiotic therapy. Aguet and Favez (1954)[7] treated 12 patients with cortisone and streptomycin and found that the clinical and radiologic results were superior to any the authors had observed with other types of treatment. In contrast to this favorable result, Des Autels and his group[8] (1956) treated 15 cases with cortisone or corticotropin in conjunction with antibiotics. Seven of these patients died during therapy. When treatment was stopped in the remaining eight patients, there was a sharp rebound phenomenon and three more died. The authors found that, while hormonal therapy resulted in an early apparent dramatic clinical improvement, x-rays showed progression of the disease in 80% of the patients.

There appears to be very little work on the effect of a combination of specific antibacterial and corticosteroid therapy in ocular tuberculosis. Pacynska[9] reports four cases of ocular tuberculosis which apparently improved markedly as a result of treatment with a hydrolysate of corticotropin and streptomycin. The period of later observation on these cases is not given.

The rationale underlying the use of corticosteroids in combination with antibacterial

therapy appears to be not only the suppression of the allergic reaction to tuberculin but also the suppression of early phagocytosis of the bacilli which may leave them vulnerable to the action of the antibacterial agents and thus promote bacteriolysis. According to this reasoning, the actual destruction of the invading tubercle bacilli by the antibacterial agent would be promoted, rather than their phagocytosis or encapsulation with resultant bacteriostasis and the danger of later relapses. If this is true, the prolonged treatment with antibacterial agents now believed necessary to effect a cure of tuberculosis might be materially shortened, and the prognosis might be improved.

If there is any merit in this hypothesis, it should be capable of experimental proof. There is probably no better place than the eye for such a demonstration: Here the degree of inflammatory reaction and the amount of therapeutic response can be accurately evaluated from day to day. To this end the following experiment was undertaken.

Technique of Experiment

On Jan. 3, 1956, seventy normal rabbits of the same race and breed were given inoculations subcutaneously in the groin with virulent human tubercle bacilli, Strain H 37 R. V. On April 4, 1956, all rabbits were tested intracutaneously with P. P. D., and all were hypersensitive in varying degrees. On April 30 all animals were given inoculations in the anterior chamber of the right eye with the proper dose of the same bacillus. The usual transient nongranulomatous inflammatory reaction (a Koch phenomenon) to the tuberculin in the inoculum appeared after 24 hours, but the eyes did not later develop tuberculous lesions. Either the culture used for inoculation was dead or the rabbits were too highly immune for the injected dose of bacilli to be effective.

Accordingly, on May 22, inoculation of the anterior chamber of the left eyes of these same animals was done with a fresh culture, and a tenfold larger dose was given. After the usual Koch reaction these eyes all slowly developed the usual type of tuberculous lesions seen in the immune-allergic rabbits. On June 12, when the disease was well established, the animals were divided into four groups, each with equal skin reactivity to P. P. D. and each with equal average ocular lesions. These four groups were thereafter handled as follows:

Group I (17 rabbits). Left untreated as controls.

Group II (18 rabbits). Treated subcutaneously with daily doses of 1.5 mg. cortisone acetate per kilogram of body weight.

Group III (17 rabbits). Treated subcutaneously with daily doses of 50 mg. of streptomycin and 11.8 mg. of isoniazid (Streptohydrozid) per kilogram of body weight.

Group IV (18 rabbits). Treated subcutaneously with daily doses of 1.5 mg. cortisone acetate, 50 mg. of streptomycin, and 11.8 mg. of isoniazid per kilogram of body weight.

Treatment was begun on June 12, 1956, and was terminated on July 26, 1956, a period of 44 days.*

The animals in the four groups were examined periodically, at first every 2 days and later at intervals of from 6 to 10 days. The degree of the ocular tuberculosis in every eye was evaluated and charted on a 1 to 4 scale, as outlined for the previous experiments in this series. After termination of treatment the rabbits were kept under observation for a further period of five months. At the end of this time they were again tested for skin sensitivity to tuberculin and then killed. At this time there were 15 survivors in Group I, 13 in Group II, 16 in Group III, and 13 in Group IV. The left eyes were removed, and the animals were autopsied and examined for visible evidence of systemic tuberculosis. The left eyes of one-half of the animals in each group were sectioned for histologic study, and the remaining eyes were used for culture to deter-

* Chas. Pfizer & Company, Inc., provided the combination of streptomycin and isoniazid used in these experiments.

mine the presence of living tubercle bacilli in the uveal tracts.

Mortality.—During the six and one-half months' period of treatment and post-treatment observation, the total mortality was as follows: Group I (controls), two rabbits; Group II (treated with cortisone), five rabbits; Group III (treated with streptomycin and isoniazid only), one rabbit; Group IV (treated with streptomycin, isoniazid, and cortisone), five rabbits. Thus there was a higher incidence of mortality in the animals receiving cortisone. This increased mortality appeared due to either the toxic or the physiologic action of the cortisone rather than to the promotion of any systemic tuberculosis. Only two rabbits in the entire series showed any evidence of pulmonary or disseminated tuberculosis. One of these rabbits was in Group I (controls), and the other, in Group II (treated with cortisone).

Results

Group I, Untreated Controls.—The control rabbits showed the usual transient allergic inflammatory reaction shown by immune-allergic rabbits after anterior chamber inoculation with tubercle bacilli. Thereafter, within one week, evidences of ocular tuberculosis began to develop. At first there was a low-grade pericorneal congestion. This was followed by the appearance of discrete tubercles on the surface of the iris, thickening and infiltration of the iris, the formation of posterior synechiae, some clouding of the cornea, and, in a few rabbits, visible tubercles in the corneal stroma with some corneal vascularization. No rabbits in this group showed any evidence of secondary glaucoma, and none developed buphthalmos. The intensity of symptoms increased for the next six weeks, up to about Sept. 1, and thereafter slowly declined. On Sept. 12 two of the fifteen survivors appeared entirely negative, and by Nov. 20 seven were free of any evidence of clinical activity. On Dec. 17 the disease in 13 was recorded as clinically inactive, and the remaining 2 showed a trace of inflammation. However, many of these eyes were scarred and showed organic changes. Figure 1 shows the clinical course of the disease in the eye of one typical rabbit in this untreated control group.

Group II, Treated with Cortisone Only.—The disease in the rabbits receiving cortisone only behaved in a very different fashion. For the first week there was an almost complete suppression of the ocular inflammation which was present when the cortisone was first given. The organic lesions and tubercle formation were not effected. Then resulted the peculiar picture of slowly progressive tuberculosis in a relatively uninflamed eye. After one week, however, the inflammatory reaction again became apparent, and thereafter it slowly increased. Within four weeks the cortisone-treated rabbits showed an inflammatory reaction and evidences of active ocular tuberculosis approximately equal to those of the untreated controls. Thereafter, while the disease in the untreated controls remained stationary or steadily decreased, the disease in the cortisone-treated animals steadily increased. Secondary glaucoma and buphthalmos began to develop. When treatment was terminated, on July 26, four of the surviving rabbits had developed buphthalmos. Four other rabbits developed buphthalmos during the first month of post-treatment observation. Three of the eight eyes with buphthalmos subsequently ruptured. When the rabbits were finally killed, on Jan. 9, 1957, eight of the final thirteen survivors still had active inflammation in the eyes, while in five the disease appeared inactive clinically. One of these rabbits with clinically inactive disease, however, had a ruptured buphthalmic eye, which was recorded as negative because the disease appeared burned out. Three of the remaining four clinically negative eyes were examined histologically, and two of these showed active tuberculous lesions. Thus, only two rabbits in this group could be classed as having the restrained self-limited disease characteristic of the untreated immune-allergic animal. Figure 2 shows the progress of one of the more severely involved animals in this group.

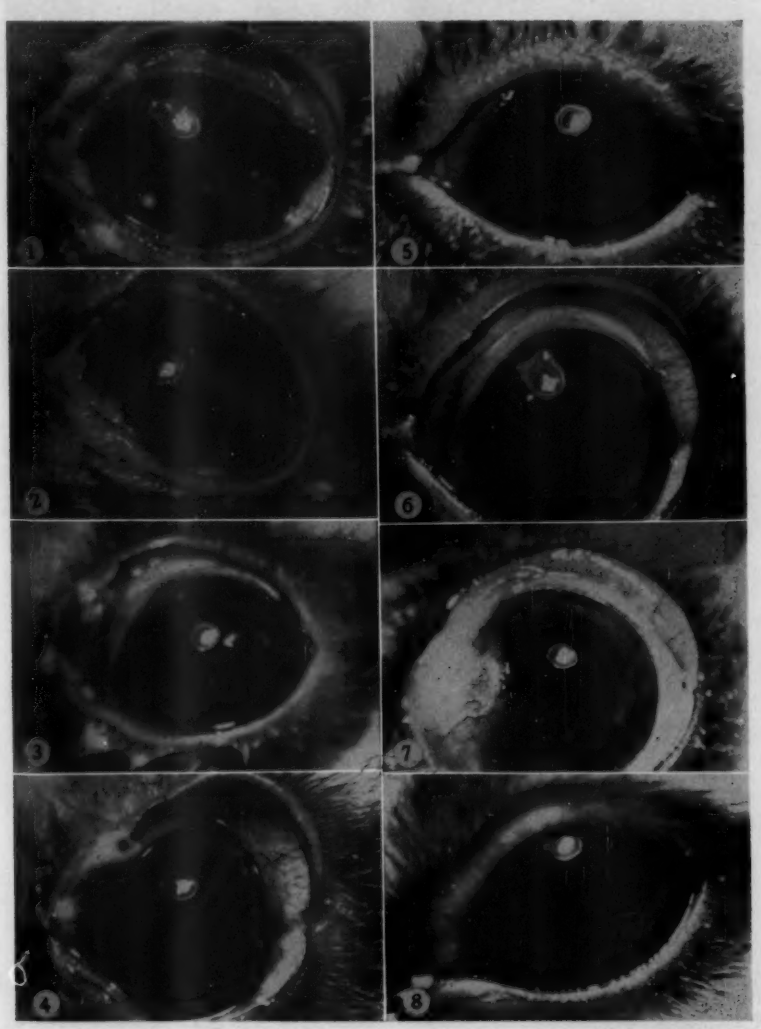


Fig. 1.—Course of tuberculosis in untreated control rabbit (Group I) from June 12, 1956, to Jan. 3, 1957, illustrating gradual absorption of the tubercles and residual scarring.

Figure 3 shows in graphic form the course of the disease in the untreated controls as compared with the cortisone-treated animals.

Group III, Treated with Streptomycin and Isoniazid Only.—The rabbits receiving streptomycin and isoniazid only showed a marked improvement in the clinical picture within 24 to 48 hours after the initiation of treatment. After two weeks' treatment the disease in 2 rabbits was entirely inactive, while in 15 it was still active. The average activity for the entire group had dropped from 1.4 to 0.7. By July 9, after 27 days of treatment, the disease in 9 of the 17 rabbits was entirely quiet and was recorded as zero, while the average activity of the entire group was 0.4. When treatment was terminated, on July 26, the disease in three of these rabbits still showed a trace of activity, but by Sept. 13 it was recorded as zero in all 17 survivors in this group. These rabbits were kept under observation for five

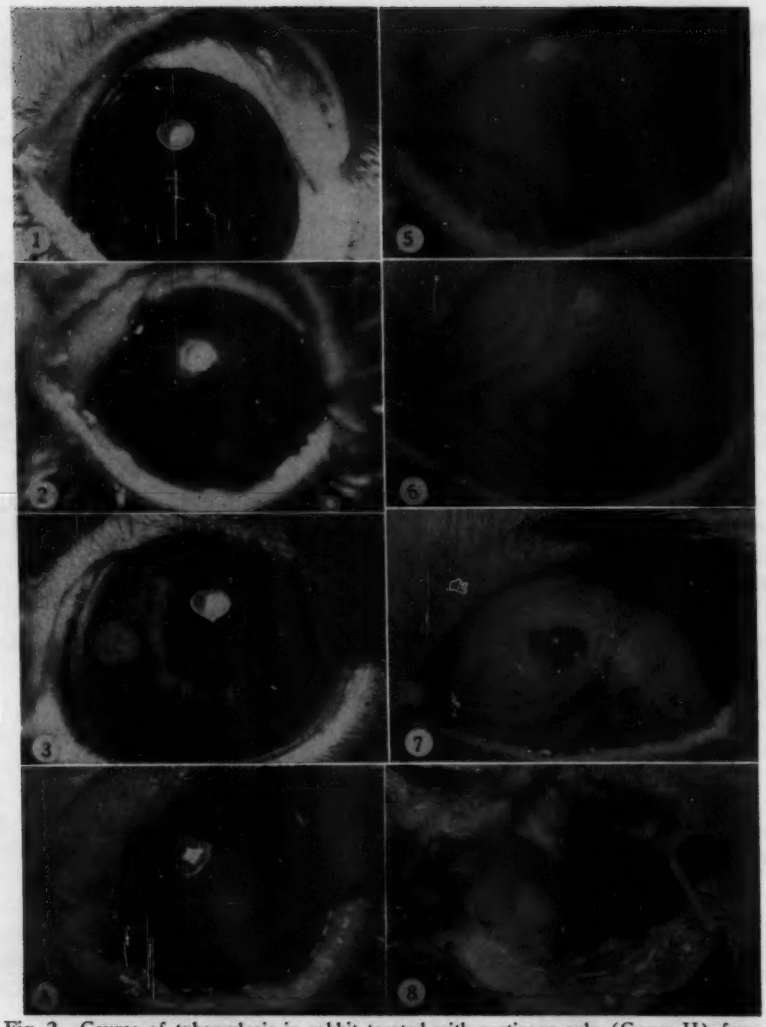


Fig. 2.—Course of tuberculosis in rabbit treated with cortisone only (Group II) from June 12, 1956, to Jan. 3, 1957, illustrating development of buphthalmos, necrosis, caseation, and rupture of the globe.

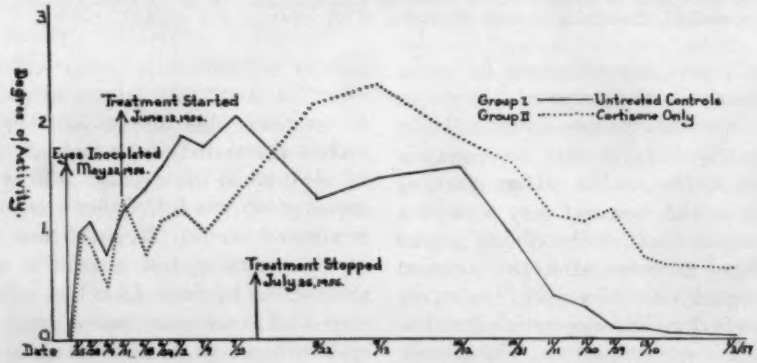


Fig. 3.—Comparison of degree of activity in untreated controls (Group I) and rabbits treated with cortisone only (Group II).

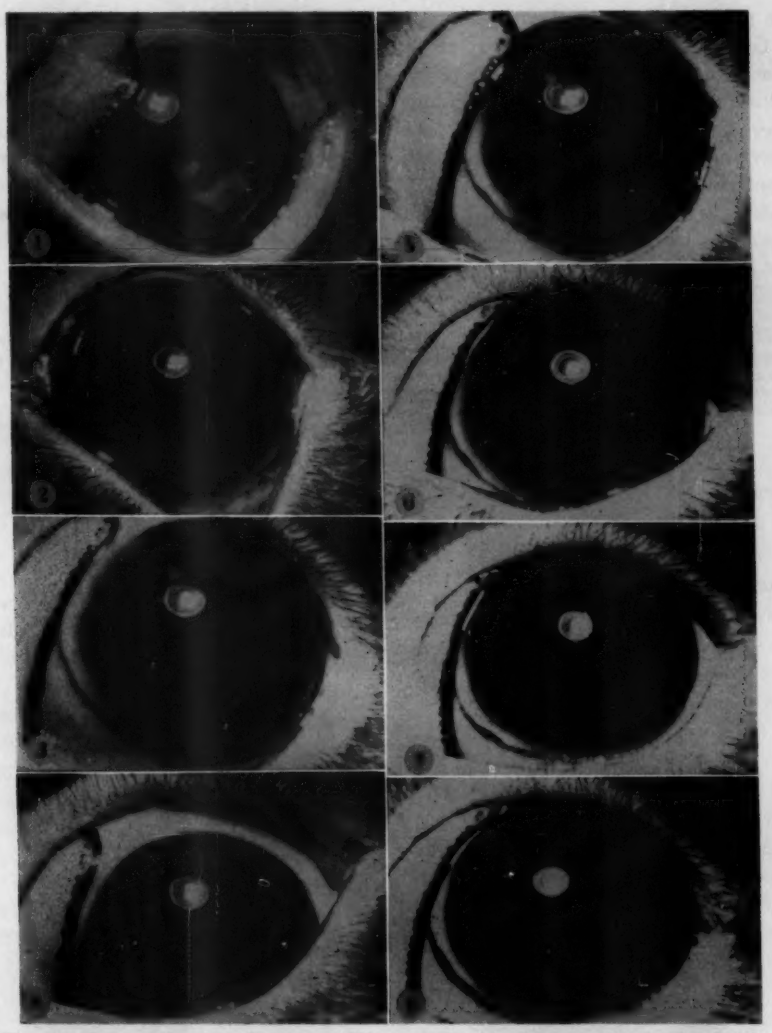


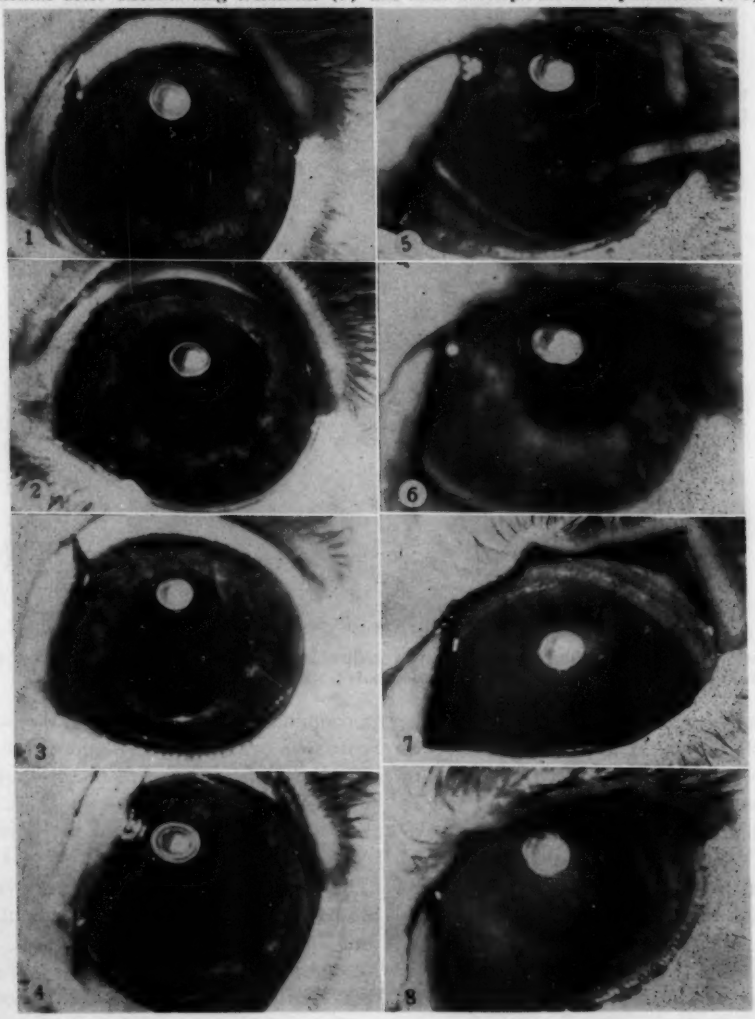
Fig. 4.—Course of tuberculosis in rabbit treated with streptomycin and isoniazid only, illustrating gradual complete healing of lesions over six-month period (Group III).

months after cessation of treatment. One rabbit with an eye in which the disease was inactive died on Dec. 17. At the time of killing, on Jan. 3, 1957, the eyes of the 16 survivors were white and free of any evidence of clinical inflammation. Figure 4 shows the progress of a most severely involved rabbit of this group.

Group IV, Treated with Streptomycin, Isoniazid, and Cortisone Combined.—The initial reaction of the rabbits treated with a combination of streptomycin, isoniazid, and cortisone was a partial suppression of the manifest inflammation. For the first month the inflammatory reaction in these rabbits was somewhat less than in the animals receiving the streptomycin and isoniazid only. The clinical picture began to improve within 48 hours after initiation of treatment. After one month of treatment, however, several of these Group IV rabbits showed a slight exacerbation, and for the next month the

average improvement was slightly less than in the Group III rabbits. However, at the cessation of treatment, on July 26, there was little difference between the two groups. The eyes of these rabbits receiving the combined treatment of cortisone, streptomycin, and isoniazid remained quiet for the next six weeks. Beginning on Sept. 15, the picture began to change. First one and then another of these rabbits began to have a relapse. By Oct. 12 there were six recidives among the 14 survivors, and by Nov. 12 a total of 8 out of 14 survivors had had relapses. Four of these relapses were only of moderate severity, but in four the relapses were severe. One of these relapsing eyes developed secondary glaucoma and buphthalmos, with final destruction of the eye. At the conclusion of the period of post-treatment observation, on Jan. 3, 1957, four of the thirteen survivors in this group had active ocular tuberculosis, while the disease

Fig. 5.—Course of tuberculosis in rabbit treated with a combination of streptomycin, isoniazid, and cortisone (Group IV), illustrating initial clearing of lesions (*1-4*), with relapse two months after discontinuing treatment (*5*) and final development of buphthalmos (*6-8*).



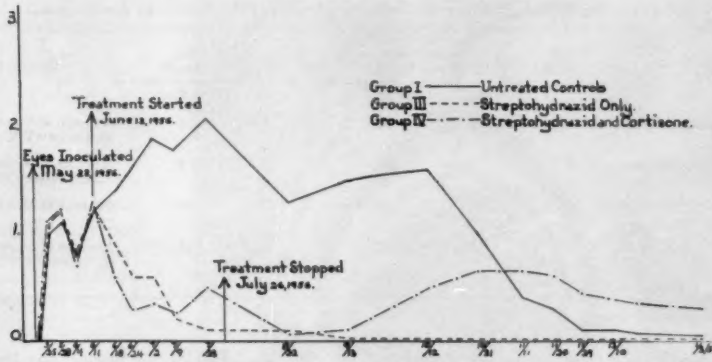


Fig. 6.—Comparison of degree of disease activity in rabbits treated with streptomycin and isoniazid only (Group III) and those treated with streptomycin, isoniazid, and cortisone (Group IV).

was inactive in nine on clinical examination. Five of these eyes with clinically inactive disease, however, showed active disease when examined histologically (see below). Figure 5 shows the progress of the tuberculosis in one of the severer recidives and shows clearly the initial apparent healing with the final relapse six weeks after termination of treatment. Figure 6 shows in graphic form a comparison of the untreated controls (Group I), of the rabbits treated with the combination of streptomycin, isoniazid, and cortisone (Group IV), and of the rabbits treated with streptomycin and isoniazid only (Group III). It illustrates well the "rebound" phenomenon after cessation of treatment. Figure 7 shows in graphic form the clinical courses of the four groups of rabbits.

Bacteriological Findings.—At the end of five months' post-treatment observation, on Jan. 3, 1957, after all animals were killed, the left eyes were removed; one-half of these (six to eight in each group) were sectioned for histologic study with use of acid-fast stains. The remaining eyes were opened aseptically; the uveal tracts were dissected out, emulsified, and cultured on Jenner's modification of Lowenstein's medium to determine the presence or absence of living tubercle bacilli. In a few instances transmission experiments in the eyes of normal rabbits were done as controls of the cultures.

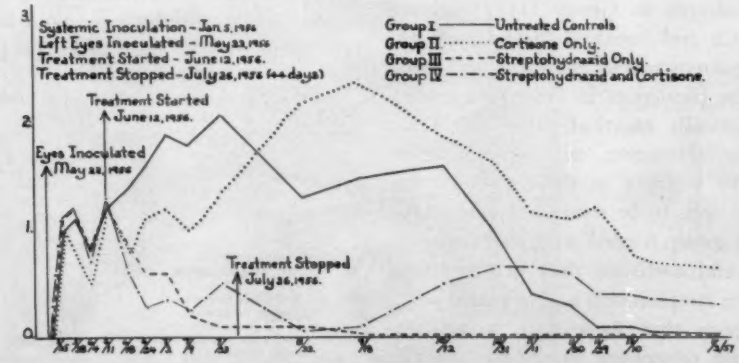

Systemic Inoculation - Jan. 5, 1956
Left Eyes Inoculated - May 22, 1956
Treatment Started - June 12, 1956.
Treatment Stopped - July 26, 1956 (44 days)
Group I ——— Untreated Controls
Group II ····· Cortisone Only.
Group III - - - - Streptohydrazid Only.
Group IV —·—·— Streptohydrazid and Cortisone.
Treatment Started
June 12, 1956.
Eyes Inoculated
May 22, 1956
Treatment Stopped
July 26, 1956.

Fig. 7.—Comparison of degree of activity in Groups I, II, III, and IV, over period of treatment and five-month period of post-treatment observation.

TABLE 1.—*Incidence of Positive Cultures for Tubercle Bacilli in Each Group*

Group	Total Cultures	Positive for Tubercle Bacilli		Negative for Tubercle Bacilli		Colony Count
		No.	%	No.	%	
I. Untreated controls	7	7	100	0	0	Average of 6 positive tubes=40; 1 tube=TNTC*
II. Treated with cortisone only	7	7	100	0	0	Average of 4 positive tubes=20; 3 tubes=TNTC
III. Treated with streptomycin & isoniazid only	8	5	60	3	40	Average of all 5 positive tubes =18
IV. Treated with streptomycin, isoniazid, & cortisone	7	4	57	3	48	Average of 3 positive tubes = 18; 1 tube=TNTC

* TNTC, too numerous to count.

Table 1 shows the incidences of positive cultures for tubercle bacilli in the four groups.

In the untreated controls (Group I) and the rabbits treated with cortisone only (Group II) all cultures were positive, the eyes containing living bacilli. Estimation of the number of colonies in the various tubes showed that in the untreated controls in six tubes the average number of colonies was 40 and in one tube they were too numerous to count. In the rabbits treated with cortisone in four tubes the average number of colonies was 20 but in the three other tubes the colonies were too numerous to count. In the over-all picture there appeared to be more colonies in the cultures from the cortisone-treated rabbits than from the controls.

In contrast to this 100% incidence of positive cultures in the control group and in the rabbits treated with cortisone only, there was a greatly decreased incidence of positive cultures in Group III (receiving streptomycin and isoniazid) and Group IV (receiving streptomycin, isoniazid, and cortisone). The incidences in these two groups were statistically identical, 60% and 57%, respectively. However, on examination of the positive cultures in these two groups there were seen to be somewhat more colonies in the group treated with streptomycin, isoniazid, and cortisone than in the group treated with streptomycin and isoniazid only. This suggests that there may have been fewer living organisms in the Group III rabbits.

This assumption is borne out by a study of the histological sections stained for tubercule bacilli by the acid-fast technique. In Group I (untreated controls) tubercle bacilli could be demonstrated in three of eight eyes; in Group II (cortisone only), in three of six eyes; in Group III (streptomycin and isoniazid only) in none of eight eyes, while in Group IV (streptomycin, isoniazid, and cortisone) bacilli were found in two of the seven eyes so stained. Thus, in Groups I, II, and IV there was little statistical difference in the incidence of stainable bacilli in the sections, while in Group III there was a marked difference, the incidence here being zero.

The ease with which bacilli can be demonstrated in stained sections is probably dependent on two factors: the number of bacilli present and the thickness and staining of the sections. Since all sections were of uniform thickness and were stained in an identical manner, the failure to demonstrate stained bacilli in sections of any of the Group III rabbits, despite the fact in five instances

TABLE 2.—*Results of Acid-Fast Stains for Tubercle Bacilli*

Group	Total Eyes Studied	Stains of Tubercle Bacilli			
		Positive		Negative	
		No.	%	No.	%
I. Untreated controls	8	3	38	5	62
II. Treated with cortisone only	6	3	50	3	50
III. Treated with streptomycin & isoniazid only	8	0	0	8	100
IV. Treated with streptomycin, isoniazid, & cortisone	7	2	30	5	70

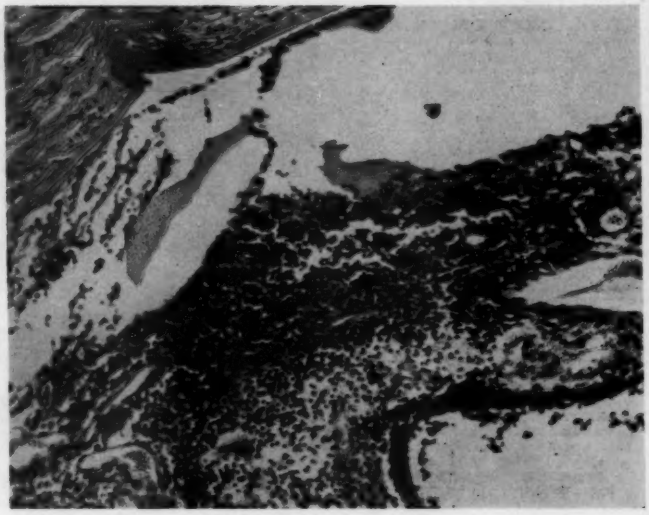


Fig. 8. — Epithelioid- and lymphoid-cell infiltration at base of iris and angle in Group I rabbit with maximum activity of the disease at time of killing.

their presence was demonstrated by culture, is strong evidence that there were few bacilli remaining in the tissues. The results of this search for bacilli in the sections are shown in Table 2.

Histology.—Group I: There were 15 survivors in the untreated control group. The eyes of six of these were sectioned for histologic study. Seven were used for culture, and two were used in another experiment.

At the time of killing two of the six eyes sectioned for histologic study showed some clinical residual activity while four appeared entirely quiet. The two clinically active eyes both showed histologic evidence of active tuberculosis—one with epithelioid- and lymphoid-cell infiltration at the angle and in the base of the iris (Fig. 8) and the other with well-formed tubercles on the anterior surface of the iris, with some scarring and nonspecific inflammation of the iris stroma (Fig. 9).

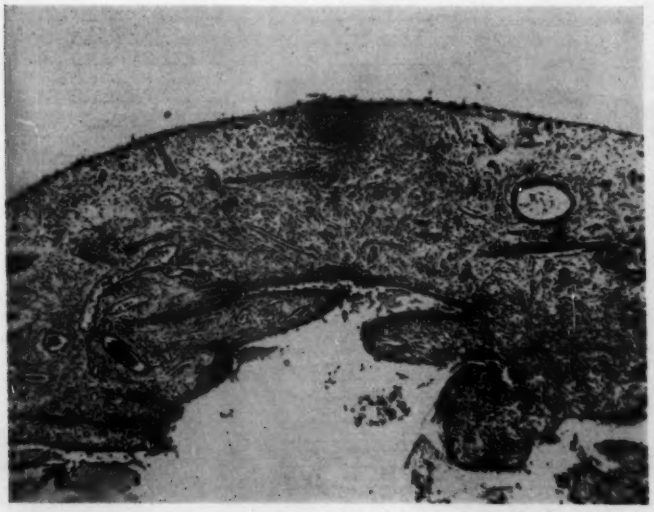


Fig. 9.—Tubercle on anterior surface of iris, with scarring and nonspecific inflammation in Group I rabbit with clinical activity of the disease at time of killing.

Fig. 10.—Scarring and minimal nonspecific inflammation in iris of untreated control (Group I) rabbit with clinically inactive disease.

Three eyes which showed no clinical evidence of active tuberculosis were likewise negative on histologic examination. All showed more or less scarring and occasionally infiltration of the iris (Fig. 10). Toward the end of the experiment, on Dec. 17, in one eye in which the disease had been recorded as clinically inactive the disease was purposely reactivated by the systemic injection of a large dose of tuberculin. After the acute focal reaction had subsided, the rabbit was killed and the eye was enucleated for histologic study. This eye showed a highly interesting picture. There were keratic deposits composed of epithelioid and plasma cells on the posterior surface of the cornea (Fig. 11) and similar collections of cells at the tip of the iris and on its surface (Fig. 12). These were highly suggestive of Koeppe and Bussaca nodules. One section of this same eye presented the unusual picture of a small clump of epithelioid cells about to break away from the tip of the iris.

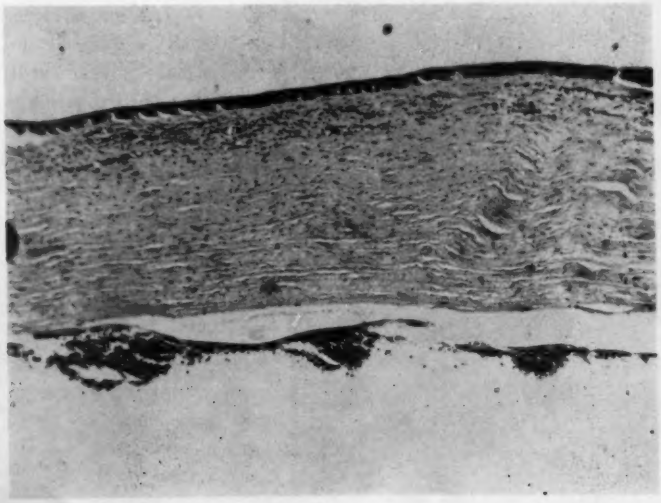


Fig. 11. — Mutton-fat keratic deposits composed of epithelioid and plasma cells on endothelial surface of reactivated eye of untreated control (Group I) rabbit.

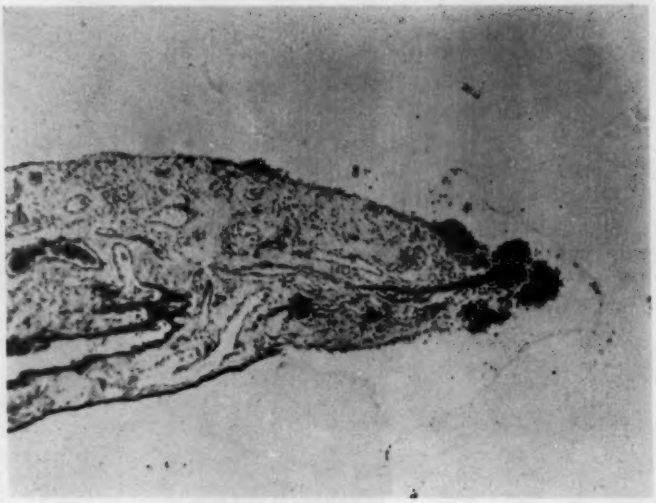


Fig. 12.—Collections of epithelioid cells on anterior surface and at tip of iris in reactivated eye of untreated control (Group I) rabbit.

Clinically it was probably a Koeppe nodule on the brink of dissolution.

Group II: There were 13 survivors in the group treated with cortisone only. The eyes of seven of these rabbits were used for culture, while six were sectioned for histologic study and stained for tubercle bacilli. One of these six eyes had developed buphthalmos and histologically showed an advanced tuberculous endophthalmitis. It was in fact little more than a mass of caseous infiltrated tuberculous tissue (Fig. 14). There were few if any giant cells in the section and no well-formed tubercles. The process had been too rapid. Cellular infiltration of the tissues with necrosis and caseation were the outstanding features (Fig. 15).

Four of the other five eyes examined histologically showed slight to moderate histologic evidences of activity, while one was negative. In the over-all picture, the reacting eyes of these Group II rabbits were more severely involved than those of the other three groups.

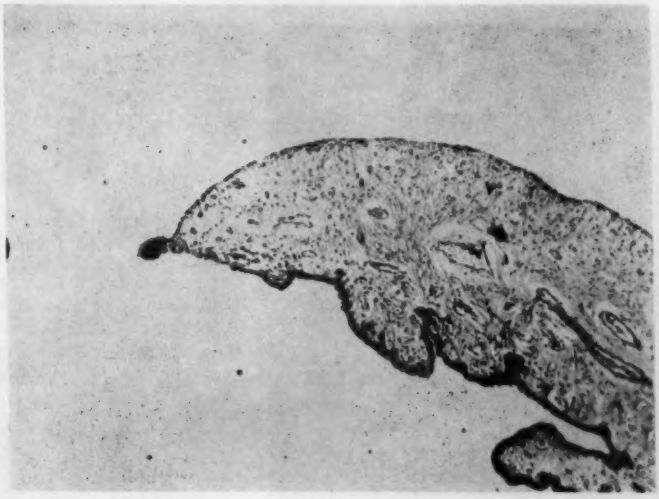


Fig. 13.—Koeppe nodule, about to break away from tip of iris, in reactivated eye of untreated control (Group I) rabbit.

Fig. 14. — Infiltrating tuberculous tissue in advanced endophthalmitis in rabbit treated with cortisone (Group II).

Group III: There were 16 survivors in the rabbits treated with streptomycin and isoniazid only. At the time of killing the disease in all these eyes was recorded as clinically inactive. The eyes of eight of this group were sectioned for histologic study. None of these eyes showed any evidence of active tuberculosis. All showed slight scarring, and several showed anterior synechiae at the angle, with a few residual cells. Figure 16 shows the most advanced of these changes. No tubercles were found in any of the sections.

Group IV: There were 13 survivors in the group treated with the combination of streptomycin, isoniazid, and cortisone. Seven of these eyes were sectioned, and six were used for cultures. One eye with advanced clinical changes at the time of killing was both cultured and sectioned. Of the seven eyes sectioned, one showed large tubercles in the ciliary region (Fig. 17) and many tubercles throughout the iris. Two other eyes, one with moderate clinical activity and one recorded as negative on clinical examination, showed a moderate degree of cellular in-

Fig. 15. — Caseation necrosis in rabbit treated with cortisone (Group II).

Fig. 16.—Anterior synechia and minimal nonspecific inflammation in rabbit treated with streptomycin and isoniazid only (Group III).

Fig. 17.—Advanced tubercle with early necrosis in rabbit treated with combination of streptomycin, isoniazid, and cortisone (Group IV).

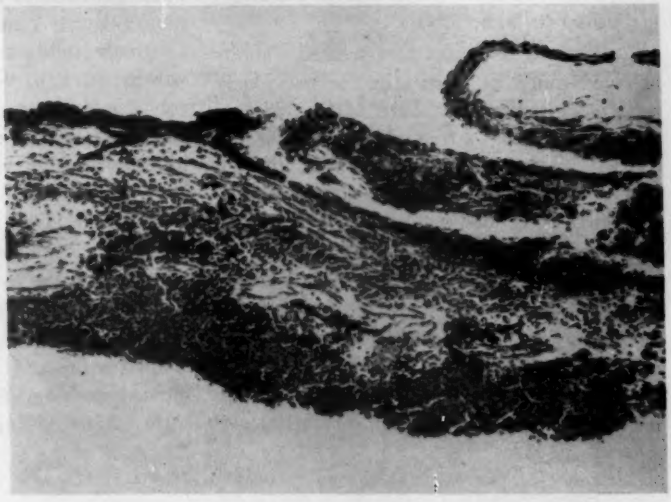


Fig. 18.—Advanced tuberculosis of iris with necrosis in rabbit treated with combination of streptomycin, isoniazid, and cortisone.

filtration in the angle and well-formed tubercles in the iris (Fig. 18). Two other eyes, both recorded as negative at the time of killing, showed minor evidences of active tuberculosis. The disease in the remaining two eyes was inactive both on clinical and on histologic examination. In summary, on histologic examination five of seven eyes from rabbits receiving the combination of streptomycin, isoniazid, and cortisone showed evidences of varying degrees of active tuberculosis.

Comment

These results speak for themselves. Ocular tuberculosis in the untreated controls followed the usual pattern of the disease in immune-allergic rabbits. It ran a restrained course for four to six months, without either secondary glaucoma or buphthalmos. At the conclusion of the experiment the disease appeared clinically inactive in 13 of the 15 survivors, while there were still evidences of smoldering activity in two eyes. However, on histologic examination evidences of active tuberculosis were found in two of five eyes in which the disease was recorded as inactive clinically. Cultures of all eyes, whether the disease was active or inactive clinically, were positive for tubercle bacilli. This persistence of living bacilli in eyes with clinically inactive disease is a good illustration of the well-known adage that apparent healing in tuberculosis is more often due to bacteriostasis than to bacteriolysis.

Disease in the cortisone-treated rabbits behaved much as it had in the previously reported experiments. Five of the original eighteen rabbits so treated died during the course of the experiment. Eight of the surviving rabbits developed buphthalmos, and three eyes had ruptured. Thus, in 8 of the 13 surviving immune-allergic rabbits treated with cortisone, what would normally have been a restrained fibrotic type of tuberculosis was transformed into a necrotizing, caseating disease which completely destroyed the eyes. Three of the remaining five survivors had either clinical or histologic evidences of severe ocular tuberculosis. In only two animals did the ocular disease follow the usual restrained course seen in immune-allergic animals.

The most striking finding in these experiments was the different behavior of the rabbits treated with streptomycin and isoniazid only and those treated with a combination of cortisone, streptomycin, and isoniazid. During the period of actual treatment there was little difference in the behavior of the two groups. All rabbits showed a prompt response to the streptomycin and isoniazid. The rabbits receiving cortisone in addition showed some early diminution of the inflammatory reaction. Thereafter there was little difference in the two groups during the period of treatment and for the ensuing month. At this time (Aug. 22) the eyes of all rabbits in both groups were free of inflammation and showed little or no clinical evidences of active disease. Had the experiment been terminated then and the animals been killed for culture and histologic study, the delayed deleterious effect of cortisone would have been missed.

Six weeks after cessation of treatment one of the rabbits which had received the cortisone-streptomycin-isoniazid combination had a relapse, and within the next month six other rabbits in this group likewise had relapses, with ciliary inflammation and the formation of fresh tubercles on the iris. An eighth rabbit had a similar relapse one month later. Four of these relapses were relatively mild, the eyes again recovering within three to four weeks, although one rabbit had a second relapse just before the conclusion of the experiment. In four rabbits the relapses were severe, the eyes being heavily involved at the time the animals were killed. One of these seven recidives developed secondary glaucoma and buphthalmos and the eye was destroyed. During this period the eyes of the rabbits treated with streptomycin and isoniazid only remained white and free of inflammation and showed nothing remotely suggesting a relapse. After killing of the rabbits, on Jan.

TABLE 3.—*Comparison of Results in Groups III and IV*

	Group IV (Treated with Streptomycin, Isoniazid, & Cortisone)	Group III (Treated with Streptomycin & Isoniazid Only)
Clinical course	All cleared under treatment; remained clear for 2 mo. thereafter	All cleared under treatment; remained clear up to killing 5 mo. later
Recurrences	In 8 of 14 survivors (57%)	None (in 16 survivors)
Histological evidence of active tuberculosis	In 5 of 7 eyes studied (70%)	None (in 8 eyes studied)
Positive cultures for bacilli	In 4 of 7 eyes cultured (57%)	In 5 of 8 eyes cultured (60%)
Demonstrable bacilli in sections	In 2 of 7 eyes studied (30%)	None (in 8 eyes studied)

3, five of the seven eyes of the Group IV rabbits which were studied histologically showed evidence of active tuberculosis. The eyes of the eight rabbits in Group III which were studied histologically showed no evidences of active tuberculosis. The incidence of positive cultures was essentially the same in the two groups, but when the sections were stained for bacilli, there was suggestive evidence that there were a smaller number of bacilli in the tissues of the Group III rabbits. These results are shown in Table 3.

This experiment was undertaken primarily to answer the question of whether the addition of corticosteroids to specific antibacterial therapy has a beneficial or a deleterious effect on the course of experimental ocular tuberculosis. The answer is clear. Under the conditions of this experiment, the addition of cortisone to specific antibacterial therapy had no beneficial effect other than the minor one of diminution of the early inflammatory reaction. It had a decidedly deleterious effect in that it promoted a high incidence of recurrences, several of which were severer than the original disease.

The mechanism whereby cortisone provoked this high incidence of recurrences is not altogether clear. Study of cortisone-treated immune-allergic rabbits in a previous experiment did not reveal any evidence of a persisting depression of the acquired systemic immunity. It is unlikely that this factor played any part in the recurrences observed in this experiment. It is theoretically possible that the cortisone in some way inhibited the antibacterial action of the streptomycin and isoniazid, but there is no actual evidence that this is so. It appears more probable that, in depressing the inflammatory reaction, the cortisone retarded the mobilization of the large macrophages and also the initiation of the fibroblastic reaction. Thus, with the suppression of these two defense factors against tuberculosis, the propagation of the bacilli was greater than could be controlled by the bactericidal action of the streptomycin and isoniazid. When treatment with streptomycin and isoniazid was stopped there were great numbers of surviving bacilli. These continued to multiply. The assault of the increased number of bacilli upon the tissues was more than the previously acquired immunity could withstand, and thereafter there were relapses. The intensity of these relapses was probably in proportion to the number of bacilli still present in the eye and the amount of resistance acquired by the individual rabbit.

The results of this study closely parallel those of a very recent experiment by Naguib and Robson.[10] These investigators studied the effect of cortisone alone and cortisone plus isoniazid on the corneal tuberculosis of both normal and adrenalectomized mice. The corneas of these mice were given inoculations of bovine tubercle bacilli. Adrenalectomy produced a slight but definite favorable effect on the course of the corneal disease. Cortisone, in both normal and adrenalectomized animals, had a slight beneficial effect for the first three weeks, in that it decreased the size of the lesion by diminishing the edema and vascularization. Thereafter, it exerted a markedly deleterious effect, with a spread of the corneal lesion, extensive necrosis, caseation, and finally perforation of the globe. There was also a systemic spread of the disease to many organs, a phenomenon which was never observed in the untreated controls. It was

further found that when animals were treated with a combination of cortisone and isoniazid the hormone neutralized the beneficial effects of the isoniazid and there was an exacerbation of the local tuberculosis and a spread of the disease to the liver and spleen of many of the animals. Histologic examination of the lesions of the treated animals showed the same marked multiplication of the bacilli as was noted in the experiment reported here.

It is of course dangerous to draw clinical conclusions from experimental observations, but in this case it appears justifiable to do so. Earlier in this report it was mentioned that clinical observations had indicated a deleterious action of the corticosteroids in clinical ocular tuberculosis. A review of the histories of private patients with granulomatous uveitis who had been referred to one of us for diagnostic study over the last few years revealed five cases, which would be classed clinically as almost undoubted ocular tuberculosis, which had been treated somewhat extensively with the adrenal corticosteroids prior to their referral. In all of these patients there had been some apparent initial improvement under this therapy. In all, however, the condition finally progressed. In three the termination of treatment was quickly followed by the so-called rebound phenomenon, in each case a relapse of such severity that vision was irretrievably damaged when the disease finally burned out or was controlled by antibacterial therapy. In all these cases the etiologic diagnosis was entirely a clinical one and is therefore subject to some uncertainty. There is no uncertainty, however, in the case of a patient recently reported by Zimmerman.[11]

His patient was a 45-year-old white farmer, with an essentially negative medical history, who had had a granulomatous iritis with secondary glaucoma over a two and one-half month period. Intensive treatment with cortisone, topically, subconjunctivally, and systemically, resulted in a control of the glaucoma and a great improvement in the iritis. All went well for awhile, when suddenly the anterior chamber deepened, the lens became dislocated, an exudate appeared in the anterior chamber, the cornea became opaque and bulged, and the tension rose sharply. The eye was then enucleated.

Histologic study showed an advanced caseous tuberculous endophthalmitis with necrosis of the retina (Fig. 19) and of the iris (Fig. 20). The ciliary body showed tubercles and giant cells (Figs. 21 and 22). Acid-fast stains showed scattered tubercle bacilli in the areas of caseation necrosis

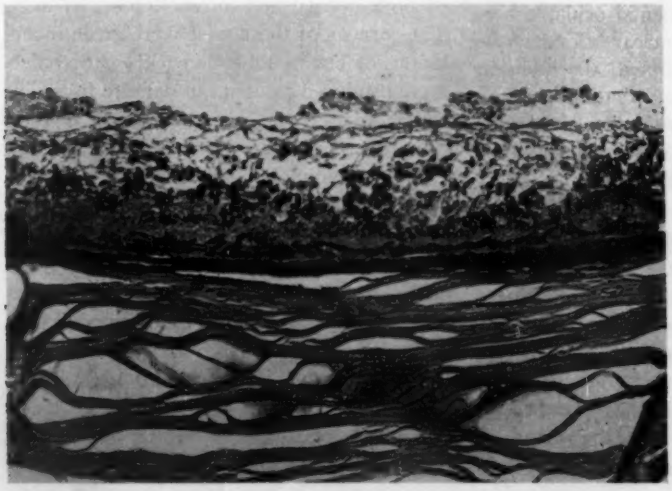


Fig. 19. — Retinal necrosis in advanced clinical tuberculous endophthalmitis. (Provided by Dr. L. R. Zimmerman.)

Fig. 20.—Advanced necrosis of iris and ciliary body in clinical tuberculous endophthalmitis. (Provided by Dr. L. R. Zimmerman.)

Fig. 21.—Tubercles and necrosis in ciliary region in advanced clinical tuberculous endophthalmitis. (Provided by Dr. L. R. Zimmerman.)

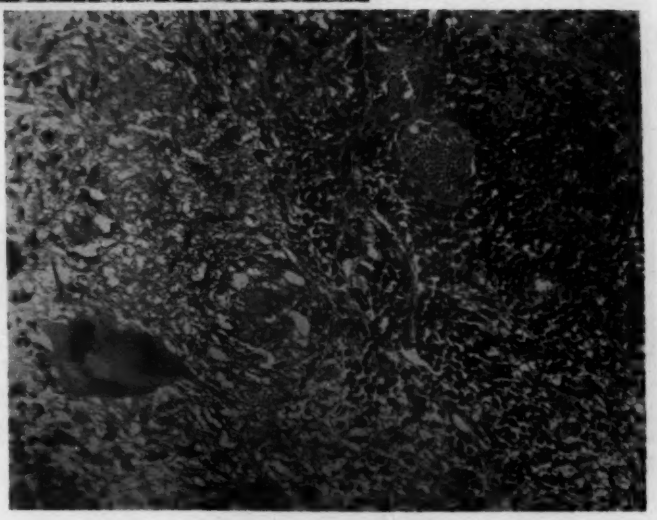


Fig. 22.—Tubercles and giant cell in advanced clinical tuberculous endophthalmitis. (Provided by Dr. L. R. Zimmerman.)

in both the anterior and the posterior ocular segments. This eye showed the same malignant, caseating, necrotizing type of tuberculosis shown by many of the immune-allergic rabbits treated with cortisone. A comparison of this eye with the eye of one of the cortisone-treated rabbits (Figs. 14 and 15) shows many points of histologic similarity in the two. In the human eye the process had been somewhat slower, while in the eye of the experimental rabbit the process had been more rapid and typical tubercles and giant cells had not had time to form. In both eyes, however, the outstanding features were the same—a rapidly developing endophthalmitis with advanced caseation necrosis.

Summary

The administration of cortisone to immune-allergic rabbits with a secondary ocular tuberculosis, transforms with is normally a restrained self-limited disease into a necrotizing, caseating process with resulting destruction of a high percentage of the eyes. This confirms a previously reported experiment.

Treatment of immune-allergic rabbits with a combination of streptomycin and isoniazid (Streptohydrazid) and cortisone did not enhance the therapeutic action of the streptomycin and isoniazid and had no beneficial effect other than the minor one of diminishing slightly the early inflammatory response.

The combined treatment had a markedly deleterious effect in that it promoted recurrences of active tuberculosis in the eyes of more than one-half of the animals so treated. These recurrences in many cases were severe, and occasionally they completely destroyed the eye.

These experiments give no support to the premise that the addition of corticosteroids to antibacterial therapy is beneficial in ocular tuberculosis. On the contrary, the results here reported sharply suggest that such combined therapy is specifically contraindicated.

Wilmer Institute, The Johns Hopkins Hospital (5).

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An Analysis of the Illumination Technique of Cibis

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Cibis recently published an account of a new technique of illumination for microscopy.[1] Figure 1 illustrates some of the major differences between microscopy with transmitted and Cibis illumination. Note how details which are not visible with ordinary illumination suddenly appear, such as zones of discontinuity in the lens. There are also striking color changes in the cornea, iris pigment, and so forth. Subtle color differences appear, for instance between ciliary muscle and surrounding connective tissue. In the present work I have attempted to analyze this method in order to be better able to interpret what is seen, to plan further applications, and to be able perhaps to extend the technique.

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From the Department of Ophthalmology, Washington University School of Medicine and the Oscar Johnson Institute.

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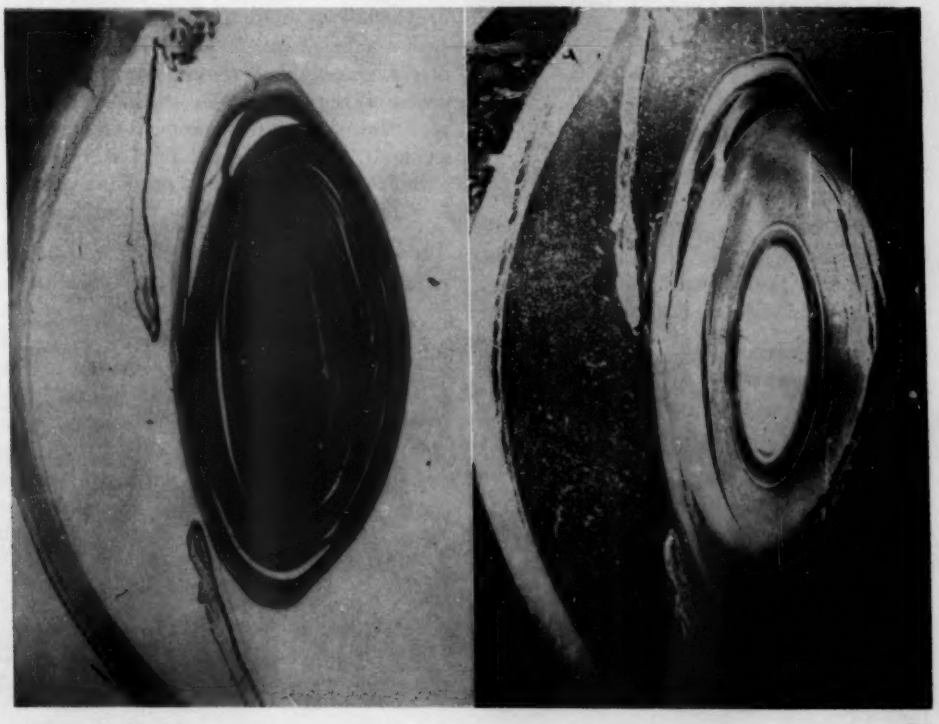
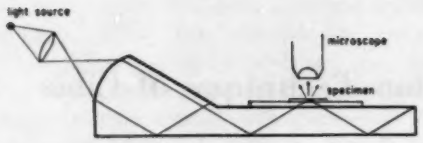
The Production of Color

Color in an object is produced by seven basic mechanisms: Light striking an object

Fig. 1.—Left, low-power photomicrograph of the anterior part of a human eye stained with eosin. Transmitted illumination used. Right, same section viewed with the oblique illumination system of Cibis. (Photograph by courtesy of Dr. Cibis.)





CIBIS SYSTEM

Figure 2

may be reflected, transmitted, or absorbed, and these may occur in a manner dependent upon wave length. Absorbed light can be re-emitted at a different wave length as fluorescence and can emerge from the object from the same side it entered (fluororemission) or from the other side (fluorotransmission). Color can also be produced by refraction, diffraction, and interference.

It has been said that wave lengths which are most strongly absorbed by an object are also the most strongly diffracted.[2] This is offered as an explanation of certain color reversals seen in dark-field illumination.

Synthesis

In Cibis' system (Fig. 2), light enters a prism whose curved face focuses it upon a glass plate. The angle at which the light strikes the plate is made acute enough that total internal reflection occurs and the light reflects its way across the plate until an object such as the specimen sends some of it off toward the observer.

The parts of the Cibis system can be eliminated one by one (Figs. 3 to 5). The simplest way to demonstrate the Cibis effect is to hold a slide in a beam of sunlight

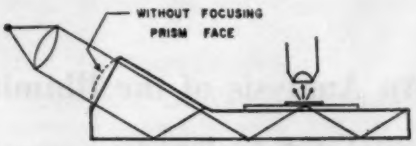


Fig. 3.—Modified Cibis system for oblique illumination.

entering obliquely through a window, so that the slide is observed against the dark field offered by the shadow below the window. The Cibis system is preferred as a convenient and efficient means of obtaining oblique illumination for use on the stage of an ordinary microscope.

Droplet Beam Analysis

If only a tiny droplet of fluid is placed between the plate and the slide, just a pencil of light will traverse the interspace and enter the slide (Fig. 6). When one is using high magnification and observing cornea, for instance, four distinct spots are seen: 1. With a dirty slide there is a point of diffuse scattering by the dirt where the droplet allows light to reach the undersurface of the slide. 2. There is an area of bright green fluorotransmission where the pencil of light traverses the eosin-stained specimen. 3. There is another diffuse scattering by dirt where the light is reflected back from the top surface of the coverslip. 4. There is another green fluororemission where the pencil of light retraverses the section.

That both fluorotransmission and fluororemission occur can be confirmed by immersing the slide in water (Fig. 7) and noting that the effects persist.

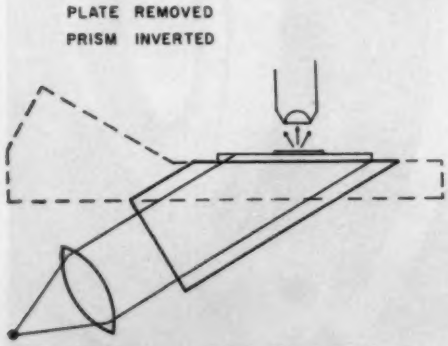


Fig. 4.—Further modified oblique illumination.

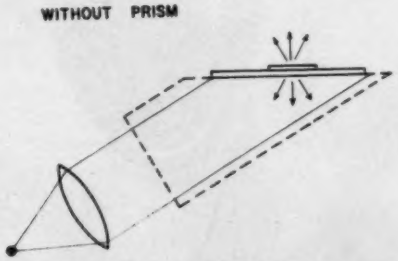


Fig. 5.—Simple oblique illumination.

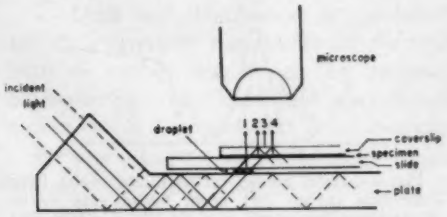


Fig. 6.—Droplet beam analysis (see text).

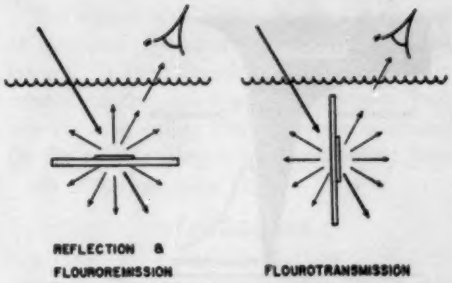


Fig. 7.—Immersed specimen.

Necessary Conditions

The internal reflections in the Cibis plate tend to polarize the light horizontally. That such polarization is not ordinarily required is shown by the fact that the plate can be eliminated (Fig. 4) without loss of the Cibis effect. This can be confirmed by depolarizing the light which enters the microscope slide. Placing a polarizing filter in front of the light source (or in the microscope), one finds that the effect is enhanced by polarizing the light vertically. Inspection shows that this is because a better dark field is obtained.

The importance of a good dark field can be demonstrated by lighting a specimen by both ordinary and Cibis techniques. By varying the strength of the ordinary light, one finds that the Cibis effect is easily completely "drowned out."

Diffraction, Interference, and Refraction

Diffraction occurs in oblique microscopic illumination and serves to emphasize boundaries. If diffraction also occurs from highly absorbent objects, it might be the explanation of the striking changes in color of pigment granules, for instance. Except as it occurs in diffraction, I have found no need to postulate interference to account for the effects of Cibis illumination. Refraction does not appear to be of importance in the production of color except when one is studying prismatic crystals.

Research Microscopes

I attempted to duplicate the effects of Cibis illumination with phase, dark-field, fluorescent, and polarization microscopy.

Phase microscopy reveals the structural detail seen with oblique illumination except for the zones of discontinuity of the lens. It does not, of course, produce the color contrasts which can be so informative with oblique illumination.

Cracks and scratches in the section or the crystalline "dirt" sometimes present on the surface of a section are rendered visible by oblique illumination by virtue of its dark-field properties and can also be seen easily with a dark-field microscope. Dark-field microscopy also reveals the zones of discontinuity of the lens.

With ultraviolet light, autofluorescence of the tissue is elicited with little if any fluorescence of the eosin, and so structural details are not seen.

Polarization microscopy is not revealing, since the lens and other eye tissues are not doubly refractile.

Eosin

I have been especially interested in the striking amount of detail seen in eye sections stained with eosin when they are viewed with oblique rather than transmitted illumination.

Eosin absorbs a narrow band of light in the blue-green region of the spectrum, with somewhat less absorption throughout the blue (Fig. 8). Thus it ordinarily appears to transmit red, but it is potentially dichroic and under certain conditions displays various shades of magenta and blue.

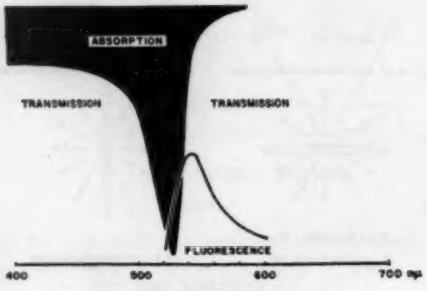


Fig. 8.—Eosin transmission—absorption and fluorescence curves. The ordinates are arbitrary, and the relative height of the two curves is only qualitatively correct.

Eosin fluoresces in the green. Thus, when stained sections are illuminated obliquely so that directly transmitted light is not seen they appear green by both fluorotransmission and fluororemission. However, thick or dense layers of eosin appear red even in oblique illumination by virtue of internal reflections and reabsorption of fluoresced light. The ease with which fluorescence effects can be drowned out by transmitted light can be appreciated from Figure 8.

Both diffusely and specularly reflected light from eosin appear green, but this may just be fluororemission. I have not been able to recognize any other color effects produced by reflection alone.

Filters

In Figure 9 the absorption and fluorescence spectra for eosin are plotted with the transmission spectra for two Kodak Wratten filters. With oblique illumination the fluorescent effects on eosin can be canceled by the use of filters which do not transmit in the green. The No. 74 narrow-band green filter permits fluorescence although it destroys all color variation. With transmitted light the No. 74 filter increases contrast monochromatically.

Lens

Some tissue sections of lenses show zones of discontinuity when viewed in oblique

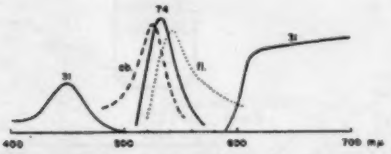


Fig. 9.—Eosin curves versus filters. (*ab*) Eosin absorption curve; (*fl*) eosin fluorescence curve; *31*, transmission curve for Kodak Wratten filter No. 31; *74*, transmission curve for Kodak Wratten filter No. 74. (Ordinates arbitrary.)

light. With high power certain zones are seen to contain hundreds of tiny granules which scatter light in the same way that dusty air scatters a beam of sunlight. Zones vary in the size and number of the granules they contain and appear red when there is so much scattering that the section is no longer effectively viewed in dark field. Under high power and oblique illumination the granules appear as tiny stars. With transmitted illumination they are seen as minute black specks. These granules are so small that oil immersion fails to resolve either their surface details or contours.

The amount of fluorescence seen in a given portion of a tissue or from one tissue to another also varies. This variation in lenses is said to correlate well with their state, cataractous ones fluorescing better than noncataractous ones.[4] Whether this variation is on a purely physical basis or whether chemical alteration of the eosin occurs in some of the stained structures is not known.

Summary

An analysis of the new technique of illumination for microscopy recently published by Cibis has shown the following:

1. Interference phenomena need not be postulated except where diffraction also occurs. Refraction likewise is of no practical significance in color production.

2. Diffraction may account for the color reversals of pigments and heavily stained objects.

3. Horizontal polarization occurs but is not necessary. The effects can be enhanced by polarizing the light vertically.

4. Dark-field illumination is produced. (*a*) It is primarily responsible for the visibility of surface details and (by contrast) of scattering. (*b*) Dark-field examination makes visible the fluorescent effect on eosin.

5. The effect of reflection alone is not known. Scattering produces obliteration of the dark field and is then seen indirectly under low power by color shifts.

6. Eosin absorbs and fluoresces light in a narrow green zone. It is therefore a dichroic transmitter (of red and blue) and a monochroic emitter (of green) and is capable of showing a variety of colors in the combination of these. Its fluorescence properties may be chemically altered in some cases.

The nature and significance of the zones of granules found in some lenses is not known. It is assumed that these zones are related to the zones of discontinuity seen biomicroscopically. Further work is needed on the submicroscopic anatomy of the lens.

640 S. Kingshighway (10).

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Infantile Cerebroretinal Lipidosis (Tay-Sachs Disease)

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The lipidoses are a group of disorders which have in common a disturbance of lipid metabolism. The lipidoses include Tay-Sachs disease, Niemann-Pick disease, Gaucher's disease, Hand-Schüller-Christian disease, and the xanthomatoses.

A specific lipid has been identified in Niemann-Pick's disease, sphingomyelin[1]; in Gaucher's disease, kerasin,[2] and in Hand-Schüller-Christian disease, cholesterol. The xanthomatoses include those lipidoses in which cholesterol is the predominant lipid.[3] In the infantile cerebroretinal lipidosis, Tay-Sachs disease, the lipid involved is a cerebroside, provisionally designated as Substance X, containing the characteristic amino acid neuramic acid.[4]

In the lipidoses the lipids accumulate in various sites, in the viscera, central nervous system, skin, and skeleton.[5] A somewhat similar tissue response occurs in all the lipidoses. The lipid is ingested by phagocytes giving rise to "foam cells," in addition to a lipid degeneration of tissue cells.[5] The lipids may be confined to reticular cells and histiocytes, notably in the liver and spleen. They may affect ganglion cells of the central nervous system. They may involve the entire body, including the central nervous system.[6]

This study concerns the type of lipidosis which occurs in infants, in which there is a striking feature of swelling of specific nerve cells with granules of a lipid nature, in the central nervous system and the retina. In the retina the specific portion that is involved is limited to the ganglion cell. This ganglion-cell lipidosis is not confined to the macula but involves ganglion cells of the entire retina. The term cerebromacular degeneration, which has been used for this disease, is apparently erroneous. Amaurotic familial idiocy, as a term, describes the effect of the disease, resulting from extensive degeneration of the central nervous system. The term Tay-Sachs disease appropriately denotes the original investigators. However, in view of our present knowledge, the name infantile cerebroretinal lipidosis seems more appropriate.

A type of retinal lipidosis occurs in 30% of cases of Niemann-Pick disease. In Niemann-Pick disease there is always added a hepatosplenic component. Not included in the designation of cerebroretinal lipidosis is Hand-Schüller Christian disease, in which there is no central nervous system involvement.[6] Spleen, skeleton, and skin, as well as the central nervous system, are affected in Gaucher's disease.[6]

A similar type of cerebroside has been identified in the juvenile form of amaurotic idiocy, or Spielmeyer-Vogt disease. This disease occurs at the age of 5 to 8 years.[18] Pigmentary changes at the macula are seen rather than the cherry-red spot which is pathognomonic of the infantile disease.[17] Pathologically there is lipid degeneration of the ganglion-cell layer of the retina.[17] However, the outer retinal layers are also involved. The rod and cone layer is disrupted, with rarefaction and narrowing of the outer nuclear layer. This is followed by irregular proliferation of the pigment epithelium and invasion of the retina by pigment granules.[17] The cerebral and spinal pathology of the juvenile form is morphologically similar to the infantile form of cerebroretinal lipidosis.

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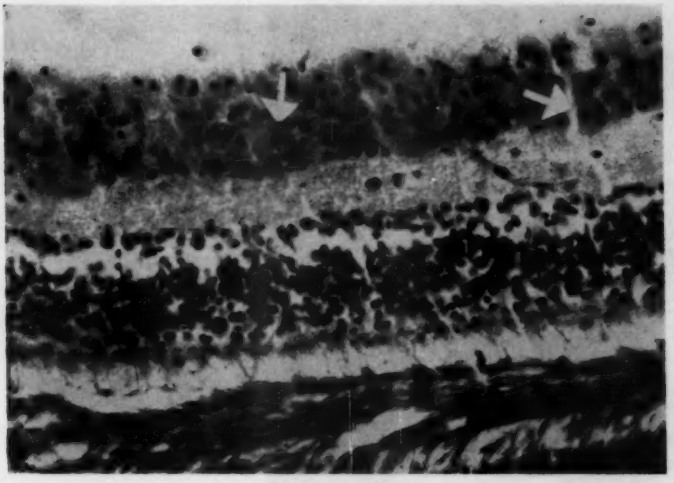

Fig. 1 (Case 1).—Age 7 months. Swollen ganglion cells, laden with lipid material, are identified throughout the ganglion-cell layer (arrows). Reduced about 37% from mag. × 360.

Nineteen cases of infantile cerebroretinal lipidosis have been previously described in the literature in which autopsies have been performed and eyes have been examined post mortem.[7-11] They have been classified under various names, such as the infantile form of amaurotic idiocy, Tay-Sachs disease, and cerebromacular degeneration. Five additional cases of infantile cerebroretinal lipidosis were studied histologically at Montefiore Hospital and form the basis of this report. The diagnosis in each case was verified at complete autopsy. The eyes were sectioned at the eye laboratory at this hospital.

Report of Cases

CASE 1.—The onset of symptoms was at the age of 3 months. A cherry-red spot at the macula was noted upon admission. The patient survived four months. Autopsy, at the age of 7 months, revealed swollen neurones with lipid material in the cerebral cortex and midbrain and in the basal ganglia. Swollen lipid-laden ganglion cells were noted throughout the retina. Partial optic atrophy was present.

CASE 2.—The onset of symptoms was at the age of 3 months. A cherry-red spot was noted at the macula. The infant survived

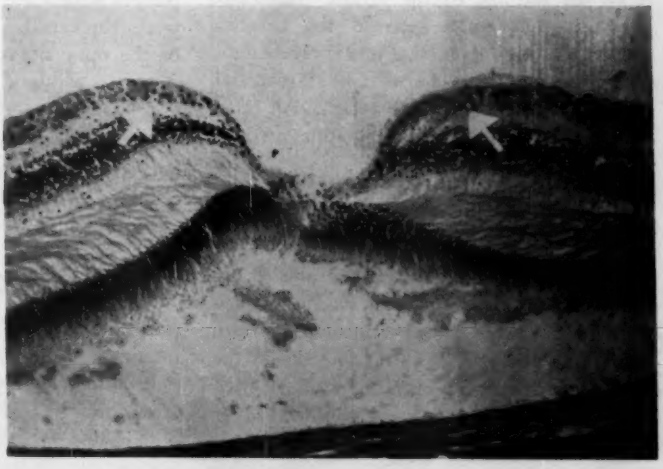

Fig. 2 (Case 2).—Age 15 months. Lipid-laden ganglion cells are seen most readily at the macula (arrows). Reduced about 37% from mag. × 120.

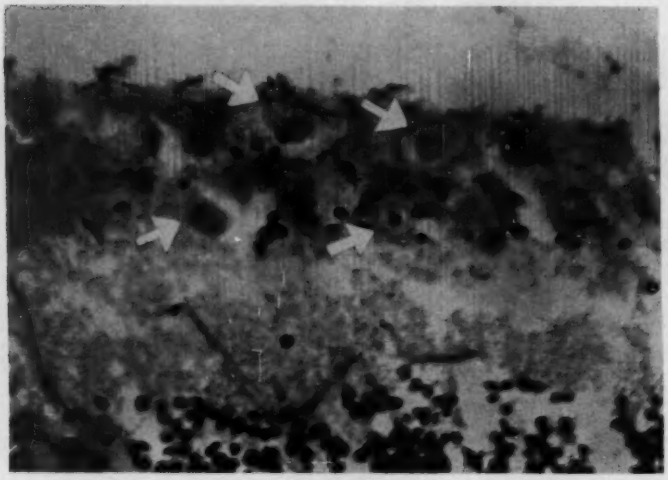

Fig. 3 (Case 3).—Age 18 months. Numerous lipid-laden ganglion cells are noted in the ganglion-cell layer (arrows). There is loss of multipolar form. The cytoplasm is granular. Small pale-staining nuclei are displaced toward the periphery of the cell. Reduced about 37% from mag. × 600.

a period of 12 months. Autopsy, at the age of 15 months, revealed a well-developed brain. Ganglion cells were swollen throughout the cerebral cortex. Swollen Purkinje cells were seen in the cerebellum. In the retina ganglion cells were swollen with lipid granules. These cells were seen throughout the macula and periphery. All other cellular layers of the retina were intact. Optic atrophy was extensive.

Case 3.—Symptoms were noted at the age of 5 months. A cherry-red spot was noted at the macula. The infant survived 13 months longer. An autopsy was performed at the age of 18 months. The brain was large for the age of the infant. Ballooned ganglion cells were seen in the cerebral cortex, basal ganglia, and cerebellum. Ganglion cells, swollen with lipid material, were noted throughout the retina. All other cellular layers were intact. Optic atrophy was prominent.

Case 4.—The age of onset of symptoms was at 6 months. A cherry-red spot was noted at the macula. The infant survived 19 months longer and died at the age of 25 months. Autopsy revealed many swollen lipid-laden cortical neurones in the cerebrum. There was atrophy of Purkinje cells in the cerebellum. Swollen neurones were identified in the brain stem. In the ganglion-cell layer of the retina many atrophic cells were seen, with numerous enlarged ganglion cells. There was a notable gliosis of the nerve fiber layer. All other cellular layers of the retina remained intact. Optic atrophy was present.

Case 5.—Symptoms were noted at the age of 6 months. A cherry-red spot was noted at the macula. The infant survived 34 months from onset of symptoms, which was the longest of the series. An autopsy was performed at the age of 40 months. Loss of substance in the white matter of the brain was noteworthy. Swollen and atrophic nerve cells were seen in the cortex and midbrain. Free fat was noted in macrophages within the brain stem. The meninges were thickened. Complete demyelinization of the optic nerve was present.

In the retina a rare swollen ganglion cell was identified. There was almost complete atrophy of the ganglion-cell layer. The nerve fiber layer was thin and gliosed. Other cellular layers of the retina were intact. Optic atrophy was complete.

Comment

As described by Sachs,[12] infantile amaurotic familial idiocy is usually restricted to infants of Jewish extraction, as were four of the five in this report. The fifth was of Italian extraction. There is a familial

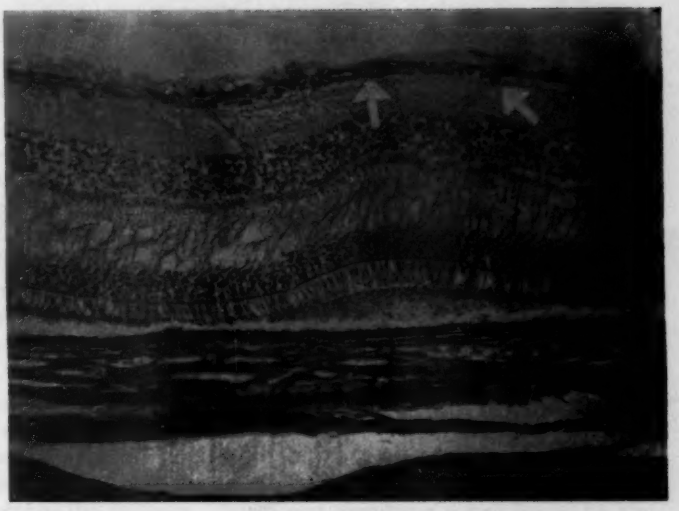

Fig. 4 (Case 5).—Age 40 months. Almost complete atrophy of the ganglion-cell layer. Only a rare swollen ganglion cell is identified (arrows). Other cellular layers of the retina are intact. Reduced about 37% from mag. × 120.

tendency. Consanguinity plays a part. There is no influence of sex. Onset is at about 4 to 6 months of age. There is deterioration of mental processes, blindness, and progressive weakness. About 12 to 18 months is the usual period of survival.[13]

The characteristic histologic feature of amaurotic familial idiocy is the infiltration of neuronal cytoplasm with a granular refringent poorly stainable lipid substance.[14] These changes occur in the cortex, basal ganglia, cerebellum, medulla, spinal cord, spinal ganglia, and ganglion cells of the retina.[13]

The retina usually shows a reduction of the number of ganglion cells. The remaining cells are swollen. There is loss of the multipolar form. The cytoplasm is granular and eosinophilic. Small pale-staining nuclei are displaced toward the periphery of the cell (Fig. 3). There is loss of Nissl substance.[11]

Changes are most readily seen at the macula, where ganglion cells are in greatest number, but degeneration of ganglion cells throughout the retina is proportionately the same (Fig. 2). The nerve fiber layer is reduced as the ganglion cells die. Gliosis follows. An occasional swollen ganglion cell is noted in the inner nuclear layer.[11] All other cellular layers are preserved. The layer of rods and cones and pigment epithelium are not affected.

The optic nerve is atrophic, with demyelinization secondary to ganglion-cell degeneration.[13] There is an increase of connective tissue, with hyperplastic septa.[9,11]

When the brain is viewed grossly, the gyri are noted as narrow.[14] The sulci are broadened, with secondary exposure of the deeper crevices. Meningeal thickening and opacification is noted. Dissection of the cortex discloses indistinct demarcation between gray and white matter. Mild ventricular dilatation may be seen.[14] Similar infiltration of lipid within the neurone of the brain occurs, with swelling and displacement of the nuclei. There is ultimate atrophy and disintegration of the neurone. With the death of the cortical neurone, there is extensive loss of white matter. With protracted survival these changes may resemble those seen in Schilder's disease.[14]

The period of survival in infantile cerebroretinal lipidosis plays a major role in determining the anatomical changes in the retina. In three patients described who survived less than 13 months, there was swelling of some of the retinal ganglion cells, alongside many normal neurones. Ballooned cells were noted throughout the retina, but

Case Reports of Infantile Cerebroretinal Lipidosis

Case	Age at Death, Mo.	Survival from Onset of Symptoms, Mo.	Retinal Pathology
1	7	4	Occasional swollen ganglion cell
2	15	12	Frequent swollen ganglion cells
3	18	13	Numerous swollen ganglion cells
4	25	19	Almost all ganglion cells affected
5	40	34	Atrophy of ganglion-cell layer

they were best seen at the macula where they are most numerous. Autopsies in these cases of brief survival reveal similar swelling of cerebral ganglion cells and an undistinguishing atrophy of the remaining central nervous system.

Retinal ganglion-cell disintegration was more advanced in the remaining two cases, with survival of 19 and 34 months, respectively (Table). In the more protracted case ganglion-cell destruction was almost complete. The ganglion layer is almost completely atrophied, with glial replacement a prominent feature (Fig. 4). In like manner, autopsy of the brain in this protracted case revealed marked degeneration of the white matter, secondary to destruction of the cerebral cortical neurones.

Careful pediatric and nursing supervision, with nasal tube and intravenous feeding and the liberal use of antibiotics, was apparently the reason for the long survival of the last case rather than any difference in the nature of the disease.

Increasing numbers of cases with prolonged survival may be anticipated. The investigator will have, thereby, increased opportunity for research in life. Bielschowsky suggested that there is lipid deposition in neurones from excess in the blood stream.[15] Schaffer, on the other hand, suggested that the lipid is a product of degeneration of the affected cell.[16] Future investigation may yield the basic mechanism of this lipid neuronal infiltration, now invariably fatal.

Some disorders cause extensive damage to many areas of the retina. Infantile cerebroretinal lipidosis is a disease with specific damage to the ganglion-cell layer of the retina. Apparently no other cells are affected in the retina.

Summary

Five cases of infantile cerebroretinal lipidosis are reported. This term denotes our present concept of the pathologic changes in cases previously called cerebromacular degeneration, infantile amaurotic familial idiocy, and Tay-Sachs disease.

The term cerebromacular degeneration is a misnomer. Degeneration is not confined to the macula but involves the entire ganglion-cell layer.

Diseased ganglion cells in infantile cerebroretinal lipidosis progress from an early stage of swelling to complete disintegration.

This is a specific disease of the retinal ganglion cell and the central nervous system.

1749 Grand Concourse (53).

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Elaboration of Bicarbonate Ion in Intraocular Fluids

V. Contribution of the Lens to the Chemistry of Aqueous Humors of the Rabbit Eye

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During the past two decades experimental and clinical investigations of the dynamics of aqueous humor formation have been largely influenced by the theories proposed by Friedenwald [1] and Kinsey.[2] Thus, the active transport of the bicarbonate ion across the ciliary epithelium into the posterior chamber is regarded as the primary and fundamental step in the secretion of aqueous humor of the rabbit eye. That the bicarbonate ion is actively transported into the posterior chamber is, however, based essentially upon the findings of Kinsey [3] that the bicarbonate ion concentration in the aqueous humor is in considerable excess of that in the blood plasma. Similarly, the aqueous humors of other animals, such as guinea pig, dog, cat, and rat,[4] have been shown to have excesses of bicarbonate in comparison with blood plasma. The existence of this concentration gradient together with the probability that the ciliary body is largely responsible for the formation of the aqueous humor has led to the widely accepted view that the elaboration of the bicarbonate ion in the posterior chamber of the rabbit eye is dependent upon the secretory activity of the ciliary body. As far as we are aware, except for a suggestion made by Kinsey [2] in a diagram that some of the bicarbonate ion in the posterior chamber of the rabbit eye is in diffusional exchange with the blood bicarbonate, the published literature has presumed that the bicarbonate in the posterior chamber is derived solely from the secretory activity of the ciliary body, as described by Friedenwald.[1] With regard to the anterior chamber aqueous humor Kinsey and Palm [5] have deduced from experimental studies with Na^{24} and thiocyanate that about 42% of the bicarbonate concentration enters by flow from the posterior chamber and 58% enters by diffusion from the blood.

Other than the above roles that the anterior uveal tissue is presumed to play in the elaboration and maintenance of the bicarbonate concentration in the aqueous humor of the rabbit eye, the possible contribution of other intraocular tissues has not been investigated. This investigation was undertaken to determine whether the lens is involved in the elaboration and maintenance of the bicarbonate ion concentration in the aqueous humor of the rabbit eye.

Procedure

The procedures of removing the aqueous humors from the anterior and posterior chambers, preparation of the arterial blood plasma, and analysis of the bicarbonate ion concentration were the same as previously described.[6] The pH of the fluids was determined under anaerobic conditions as previously described.[6]

Production of Massage Cataracts.—The rabbits were anesthetized by the intravenous injection of pentobarbital sodium. Tetracaine (Pontocaine) hydrochloride (0.5%) was instilled in the lower conjunctival cul-de-sac, and a small incision in the cornea, about 1 mm. from the limbus, was made with a narrow keratome. The anterior surface of the lens was gently massaged for three to five minutes with an iris repositor. After

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completion of the procedure the anterior chamber was irrigated with isotonic saline; the iris was reposited, and atropine was dropped into the eye. The cornea was not sutured. In order to achieve rather complete opacification of the lens, the procedure was repeated three to five times at intervals of from two to three weeks.

Slit-lamp examination two weeks after the final massage and one day before chemical analysis of the aqueous humors revealed the anterior lens capsule and anterior cortex to be completely opaque, except for a clear transparent ring just below the epithelium around the equator, approximately 0.5 mm. deep. A few spots of uveal pigment were visible on the anterior lens capsule, but there were no evident signs of active iridocyclitis. The pupil was fairly active. In a few animals the anterior chamber appeared to be somewhat shallow.

Intraocular pressure of the cataractous eye, as measured by the Schiøtz tonometer, two weeks after the final massage procedure, was within the normal range and essentially similar to the intraocular pressure of the contralateral, untreated, normal eye, used as a control.

Lens Extraction.—The rabbits were given an intravenous injection of pentobarbital sodium and a retrobulbar injection of procaine (Novocain) and epinephrine (1:50,000). The pupil was dilated by the drop instillation of 1% atropine. Tetracaine hydrochloride (0.5%) was instilled into the lower conjunctival cul-de-sac. Without a prior conjunctival flap, a keratome section was made 1 mm. inside the limbus. The section was enlarged to 180 degrees by corneal scissors.* The anterior capsule was stripped off with a cystotome and capsulotomy forceps, and the lens nucleus and cortex were expressed with a lens expresser and spoon.† The anterior chamber was thoroughly irrigated with saline in order to remove as much cortical material as possible. The iris was reposited, and the cornea was sutured by four or five postplaced corneal-scleral 000000 chromic surgical (gut) sutures. A small bubble of air was introduced into the anterior chamber.

Postoperatively atropine and erythromycin (Erythrocin) ointment were applied locally, and penicillin was given intramuscularly during the first seven days, or until all signs of uveitis had disappeared. In all cases a peripheral anterior synechia was present in the area of the wound. No evidence of retinal detachment or vitreous degeneration could be detected by ophthalmoscopy or slit-lamp examination.

In some animals the intraocular pressure of the eye operated on, as measured with the Schiøtz tonometer, was lower than that of the contralateral, not operated on, normal eye.

The aqueous humors were removed four to five weeks after the lens extraction and analyzed. The eyes were enucleated some three weeks later for gross and histologic examination. In only one case was a gross detachment of the retina present. Some cortical material and posterior capsule remained in all cases. The vitreous body and retina were healthy; there were no signs of inflammation in the iris, ciliary body, or optic nerve. There was no evidence of any choroidal or subclinical retinal detachment.

Results

Bicarbonate Ion Concentration.—Normal and Cataractous Eyes (Table 1): In 9 of the 10 animals used the bicarbonate concentration of the aqueous humor in the anterior chambers of the normal eyes was higher than that in the opposite, cataractous eyes. The average difference between the two eyes was 5%, which is just statistically significant within 95% confidence limits.

* Initially peripheral iridotomy was performed on a few eyes. However, in most cases a simple extraction was performed through a dilated pupil. The iridotomy had no apparent effect upon the bicarbonate concentration of the aqueous humor as determined by experiments in which only iridotomies, without lens extraction, were performed on control eyes.

† All attempts to achieve an intracapsular extraction failed.

TABLE 1.—*Bicarbonate Concentration of Aqueous Humors of Rabbit Eye With and Without Cataract*

Bicarbonate Concentration, mM./L.							
Anterior Chamber				Posterior Chamber			Arterial Plasma
O. D. *	O. S.	Ratio †		O. D.	O. S.	Ratio	
33.5	31.4	1.066		38.2	37.2	1.027	22.6
29.8	29.4	1.013		--	--	--	20.0
33.4	33.1	1.009		39.7	42.1	0.943	26.6
32.3	31.2	1.035		32.6	37.7	0.865	22.2
30.9	27.4	1.128		34.0	37.3	0.912	21.4
29.1	28.6	1.017		39.4	32.7	1.205	20.9
30.2	26.7	1.131		39.1	32.8	1.192	14.4
26.7	25.4	1.051		32.4	35.5	0.913	15.6
31.8	28.1	1.132		40.3	38.4	1.049	21.2
--	--	--		32.9	32.4	1.015	19.6
24.8	26.9	0.922		31.4	35.1	0.895	18.9
Av.	30.3	28.8	1.050	36.0	36.1	1.002	20.3
S. D.	2.67	2.31	0.069	3.42	2.89	0.110	3.14
S. E.	0.845	0.731	0.0218	1.08	0.915	0.0348	1.00

* O. D., normal eye; O. S., cataractous eye.
† Ratio of O. D. to O. S. values.

The absolute difference (1.5 mM. per liter) represents 5% of the total bicarbonate concentration (30.3 mM. per liter) and 15% of the excess (10 mM. per liter) normally existing in the anterior aqueous humor over that of the arterial blood plasma. In the same animals the bicarbonate concentration in the posterior chamber aqueous humor was, on the average, not affected by the presence of the cataract.

Normal and Aphakic Eyes (Table 2): In all seven animals studied the bicarbonate ion concentration in the aqueous humors of the normal eyes was significantly higher than in the opposite, aphakic eyes. In the anterior chamber fluid the average difference between the two eyes was 8%, while in the posterior chamber fluid the average difference was 13%. The absolute difference in the anterior chamber fluid (2.3 mM. per liter) represented 7% of the total bicarbonate concentration in that chamber and 22% of the excess bicarbonate concentration (10.5 mM. per liter) over that in the arterial blood plasma. In a separate series of experiments with 14 other rabbits (Table 3) the bicarbonate concentration in the aqueous humor of the anterior chamber of the normal eyes was higher than in the opposite, aphakic eyes by 8%. The absolute difference in the posterior chamber fluid (4.3 mM. per liter) represented 11% of the total bicarbonate concentration in that chamber and 25% of the excess concentration (16.9 mM. per liter) over that in the arterial blood plasma.

TABLE 2.—*Bicarbonate Concentration of Aqueous Humors of Rabbit Eye With and Without Lens*

Bicarbonate Concentration, mM./L.						
Anterior Chamber			Posterior Chamber			Arterial Plasma
Normal *	Aphakic	Ratio †	Normal	Aphakic	Ratio	
33.9	30.8	1.101	43.2	38.9	1.111	24.3
31.8	30.6	1.039	40.0	32.7	1.223	15.6
35.3	32.3	1.093	39.8	34.0	1.171	23.9
33.0	29.9	1.104	39.7	34.1	1.164	23.0
29.6	27.5	1.076	38.8	34.6	1.121	21.0
30.7	30.1	1.020	35.8	33.9	1.056	23.3
31.7	28.8	1.101	33.6	32.0	1.050	21.6
Av.	32.3	30.0	1.076	38.7	34.3	1.128	21.8
S. D.	1.51	1.41	0.036	2.89	2.27	0.059	2.76
S. E.	0.570	0.532	0.0136	1.091	0.857	0.0223	1.045

* O. S., normal eye; O. D., aphakic eye.
† Ratio of normal to aphakic values.

The pH of Normal and Aphakic Eyes (Table 4): The average pH of the anterior aqueous humors from eight aphakic eyes was 0.051 units lower than in the opposite, normal eyes. This slight difference, however, was not statistically significant.

TABLE 3.—*Bicarbonate Concentration of Aqueous Humor in Fourteen Other Rabbits With and Without Lens: Summary of Results*

	Bicarbonate in Anterior Chamber, mM./L.		
	Normal *	Aphakic	Ratio
Av.	29.7	27.5	1.080
S. D.	2.40	2.40	0.130
S. E.	0.651	0.652	0.035

* O. S., normal eye; O. D., aphakic eye.

TABLE 4.—*pH of Aqueous Humor of Anterior Chamber of Rabbit Eye With and Without Lens*

	pH of Anterior Chamber Aqueous			
	Normal *	Aphakic	Dif.	Blood †
	7.611	7.596	−0.015	7.393
	7.552	7.563	+0.011	7.355
	7.531	7.561	+0.030	7.363
	7.642	7.468	−0.174	7.350
	7.580	7.467	−0.113	7.404
	7.622	7.538	−0.084	7.379
	7.646	7.489	−0.157	7.486
	7.507	7.594	+0.087	7.468
Av.	7.586	7.535	−0.051	7.400
S. D.	0.031	0.049	0.088	0.040
S. E.	0.0113	0.0173	0.0312	0.0141

* O. S., normal eye; O. D., aphakic eye.
† Arterial whole blood.

Comment

The results of this investigation clearly indicate that the bicarbonate concentration in the aqueous humor of a rabbit eye whose lens has been either made cataractous by massage or removed is significantly lower than that in the opposite, normal eye. Because of the interdependent relationship between the chemical properties of the aqueous humor and the functioning of the lens, it is reasonable to assume that under the experimental conditions the metabolic activity of the lens was effectively eliminated as a factor contributing to the chemistry of the aqueous humor. This presupposes, of course, that normally the metabolic activity of the lens appreciably contributes to the bicarbonate concentration of the aqueous humor. The most direct way for this to be accomplished is for CO_2 produced by the lens to be converted into bicarbonate into the aqueous humor.

The available experimental evidence suggests that the normal transparent rabbit lens has the capacity to contribute significantly to the bicarbonate concentration of the aqueous humor. Huysmans and Fischer [7] demonstrated that explanted rabbit lenses (306 mg. and 427 mg. wet weight) incubated in phosphate buffer at pH 7.2 at 37.5 C in the presence of 100 mg. of glucose per 100 cc. consumed 0.105 to 0.126 mg. of O_2 in six hours. With a respiratory quotient of 1 for the lens it can be shown that under the experimental conditions 0.04 to 0.05 micromoles of CO_2 was formed per minute. Similarly, Ely [8] observed that the average Q_{O_2} (microliters of O_2 consumed per milligram of dry weight per hour) for 25 explanted lenses (average estimated wet weight, 300 mg.) maintained in Ringer's solution at pH 7.35 at 37.5 C was 0.09, which is equivalent to the formation of CO_2 of 0.0063 micromoles per minute. On the basis that the rate of formation of aqueous humor in the rabbit eye is about 3.5 microliters per minute [9] and that the bicarbonate concentrations in the aqueous humors of the anterior and posterior chambers are 30 mM. per liter and 36 mM. per liter, respectively, it can be calculated that the rate of turnover of bicarbonate by flow in the two chamber fluids is, respectively, 0.105 and 0.126 micromoles per minute. Thus, according to Huysmans and Fischer's [7] data rate of formation of CO_2 by the explanted rabbit lens amounts to about 43% of flow rate of bicarbonate in the anterior chamber and 26% of the flow rate of bicarbonate in the posterior chamber, while according to Ely's [8] results these two values are 6% and 5%, respectively.† Furthermore, since the experimental conditions of the above investigators were undoubtedly suboptimal, for example, with respect to necessary co-factors and other ingredients normally present in aqueous humor as well as any possible physiologic regulator of metabolism, the actual values for the production of CO_2 in vivo may be higher. These experimental findings together with the evidence [10,11] of the presence of carbonic anhydrase in the rabbit lens suggest that the metabolic activity of the lens may contribute to the bicarbonate concentration of the aqueous humor.

From a more dynamic viewpoint, the metabolic activity of the lens may influence the forces responsible for the elaboration of the bicarbonate ion in the aqueous humors. Thus, the continuous discharge of metabolic acids, chiefly lactic,‡ from the lens into the aqueous humor § requires that the latter continuously provide the buffering capacity to neutralize the pH-lowering-effect of the acid. The elaboration and maintenance of the relatively high bicarbonate concentration in

† These differences may be due to the different incubation media employed by the investigators and to the fact that in the experiments of Huysmans and Fischer no particular caution was observed to prevent rupture of the capsule. Injury to the lens capsule leads to an increase in oxygen uptake.

‡ Huysmans and Fischer [7] and Merriam and Kinsey [12] showed that explanted rabbit lenses maintained at 37 C in phosphate buffer or in cattle aqueous humor produced 0.015 micromoles of lactic acid per minute.

§ Weekers [13] demonstrated that lactic acid is freely diffusible into and out of the rabbit lens.

the aqueous humor, therefore, may reflect, in part, a physiologic response to the acid products of lens metabolism. In this connection, Davson [14] first suggested that the high concentration of bicarbonate in the aqueous humor of some experimental animals was related to the metabolic activity of the intraocular tissues—lens, cornea, and retina—and served essentially as a buffering mechanism against the formation of acid metabolites by these tissues.

In accordance with the physiologic relationship presumed to exist between the metabolism of the lens and the forces responsible for the high concentration of bicarbonate ion in the aqueous humor, a suppression of the continuous discharge of lactic acid from the lens, associated with massage cataract [15] or lens removal,[16] should elicit a decrease in the rate of elaboration of bicarbonate ion in the aqueous humor, with a resultant fall in the concentration. This could, of course, be accomplished without any appreciable effect upon the pH of the aqueous humor. The observed lowering of the bicarbonate concentration of the aqueous humor without a significant effect upon the pH is consistent with the above expectations. The fact that the presence of the cataract had no appreciable effect upon the bicarbonate concentration in the posterior chamber and only a slight effect upon that in the anterior chamber suggests that the production of the massage cataract was not accompanied by any extensive suppression of the metabolic activity of the lens.

It is at once apparent from the above discussion that the two indicated ways in which the metabolic activity of the normal lens can influence the bicarbonate concentration of the aqueous humor may tend to cancel each other. Thus, the formation of CO_2 and its subsequent conversion to bicarbonate tend to increase the concentration in the aqueous humor, while the production of lactic acid tends to decrease the concentration. The data of Huysmans and Fischer [7] are insufficient to provide quantitative accuracy in the resolution of this problem, while the more refined and extensive experiments of Ely [8] did not include the simultaneous determination of lactic acid production by the lens with which to compare the production of CO_2. The observations of Kinoshita,[17] on the other hand, provide a more reliable basis for the quantitative evaluation of the relative contributions of the above-described mechanisms by which the metabolic activity of the lens influences the bicarbonate concentration of the aqueous humor. After establishing that the production of CO_2 by the bovine and rabbit lens occurred almost wholly via the direct oxidative route, rather than by the citric acid cycle, Kinoshita concluded from experiments with 1-C^{14} glucose and 6-C^{14} glucose that the ratio of lactic acid produced to CO_2 formed was 8:1; in other words, for every four molecules of glucose utilized to produce eight molecules of lactic acid, one molecule of glucose was shunted through the direct oxidative route, with the formation of one molecule of CO_2. These results, therefore, indicate that the metabolic acids of the lens tend more to neutralize the bicarbonate of the aqueous than the formation of CO_2 contributes to the concentration. This relationship is indeed consistent with the concept that the metabolic activity of the lens is predominantly anaerobic in nature.

From the available evidence, therefore, it seems reasonable to conclude that, while the normal metabolic activity of the lens may contribute directly a small but significant quantity of bicarbonate to the aqueous humor, the major effect upon the latter is determined by the metabolic acids released. The continuous discharge of lactic acid, by the lens, for example, is partly responsible for the relatively high bicarbonate concentration required in the aqueous humor. By the same token, the observed fall in the bicarbonate concentration of the aqueous humors attendant upon the elimination of the metabolic activity of the lens is assumed to be primarily related to the decreased rate of elaboration of the bicarbonate ion as a result of the decreased demand. The fact that the pH of the aqueous humor of the

anterior chamber remained essentially unchanged is consistent with this concept. Confirmation of this concept, however, depends upon the measurement of the rate of elaboration of bicarbonate ion in the aqueous humors under the given experimental conditions. These experiments are now in progress.

The findings of this investigation are of especial interest with regard to our understanding of the factors responsible for the formation of aqueous humor. Although considerable attention has been given to the primary role that the elaboration of the bicarbonate ion by the ciliary body may play in the secretion of aqueous humor, direct experimental evidence for this concept is lacking. The experimental conditions of the present investigation offer a unique opportunity of verifying this basic postulate of the secretion-diffusion theory. For, if the rate of elaboration of the bicarbonate ion in the aphakic aqueous humor is decreased, then measurement of the rate of aqueous humor formation would provide a good basis for experimental testing of the relationship of these two events. Experiments along these lines are in progress.

Summary

The bicarbonate ion concentration of the aqueous humors of normal rabbit eyes was compared with that of eyes in which the lens was made cataractous by massage or removed by extracapsular extraction.

The bicarbonate concentration of the aqueous humors of the normal rabbit eye was higher than that in the aphakic eyes (by 8% in the anterior chamber and 13% in the posterior chamber), and higher by 5% than that in the aqueous humor of the anterior chamber of the cataractous eye. The presence of the cataract had no effect upon the bicarbonate concentration in the posterior chamber.

The possible ways by which the lens could contribute to or influence the bicarbonate concentration of the aqueous humors are discussed. On the basis of the available evidence it is reasonable to conclude that, while the normal metabolic activity of the lens may contribute directly a small but significant quantity of bicarbonate to the aqueous humor, the continuous discharge of lactic acid into the aqueous humor requires a constant elaboration of bicarbonate to neutralize the metabolic acid. It is, therefore, suggested that the observed lowering of the bicarbonate concentration of the aqueous humors was a direct consequence of the suppression of active transfer of the ion into the aqueous humor attendant upon the removal of the lens.

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Osmolarity in the Normal State and Following Acetazolamide

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Investigations of the normal osmolar relationship between aqueous and plasma have demonstrated an aqueous osmolar excess in several mammalian species.[8,17,24,25] This excess is considered to be the dominant driving force in aqueous humor formation.[1,16,19] As acetazolamide significantly decreases the aqueous flow rate,[4-6,21] an alteration in the aqueous-to-plasma osmolar relationship might reasonably be expected following the administration of the drug. Urrets-Zavalia and Remedi [27] have demonstrated a lowering of the osmolar concentration in the dog aqueous following administration of acetazolamide, on the basis of alterations in electrical conductivity. However, no associated plasma values are reported. The present investigation has been undertaken as a further study of the aqueous-to-plasma osmolar relationship.

Method

Adult male albino rabbits weighing from 2.5 to 3.5 kg. were utilized, and each eye was used only once for aqueous puncture. They were allowed food (Wayne Rabbit Pellets) and water without restriction. Twenty-four hours before use they were transferred from the regular animal room to an air-conditioned laboratory where all experimental procedures were ultimately carried out. Six adult mongrel dogs of both sexes, weighing from 13 to 18 kg., were also utilized.

Acetazolamide was administered as a 10% solution of a sodium salt in distilled water. Rabbits received a single dose of 100 mg. per kilogram of body weight intraperitoneally. Dogs received a single dose of 50 mg. per kilogram of body weight intravenously. Isotonic saline was administered to rabbits intraperitoneally in a single dose of 1 ml. per kilogram of body weight.

All procedures were carried out on the restrained conscious animal, with use of topical tetracaine (Pontocaine) anesthesia. Blood samples were obtained with a heparinized syringe by cardiac puncture in rabbits and venipuncture of the foreleg in dogs. All syringes were lightly coated with a silicone lubricant to minimize evaporation and carbon dioxide loss. The blood samples were immediately centrifuged anaerobically, and a plasma sample was then withdrawn into a second tuberculin syringe. All samples were weighed to an accuracy of 0.1 mg.

In all cases control blood and aqueous samples were initially withdrawn from the right eye. After an interval of four to five days, acetazolamide or saline was administered and a second set of blood and aqueous samples was subsequently removed from the left eye. The time interval following the control sampling was allowed in order to minimize the disturbing effects of the initial cardiac and aqueous punctures.

Freezing-point depressions were determined with the Fiske osmometer. A 0.2 ml. sample was utilized, and all analyses were

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performed within 30 minutes of the sample withdrawal. Three readings of each sample were obtained within two to three minutes. The instrument error was determined by a comparison of the results from sample pairs of a standard solution in the normal range. The mean absolute difference between members of each pair was 0.5% of the mean standard value for eight pairs. According to Meschia and Barron,[22] the error from carbon dioxide loss is negligible. Osmolal concentrations were calculated with osmotic coefficients based on the freezing-point data of the International Critical Tables [29] and a cryoscopic constant for water of 1.86. As Smith [26] has pointed out, these osmotic coefficients refer to osmotic activities at 0 to −2 C and not at 37.5 C. If the activity is temperature-dependent, the present coefficients must be used with reservation.

Tonometry was done on the restrained animal with a calibrated Schiøtz tonometer and a 5.5 gm. weight. Results are reported in scale units.

Concentrations are expressed as millimoles or milliosmoles per kilogram of water, with assumption of a 7% solid content for plasma and negligible content for aqueous. Statistical analysis included calculation of the standard deviation and standard error of the mean and use of Fisher's *t*-test for the determination of the significance between means.[10]

TABLE 1.—*Normal Osmolal Concentrations in the Rabbit* *

Rabbits, No.	Osmolal Concentration, mOsm./Kg. of Water		
	Aqueous	Plasma	Aq.—Pl.
55	300.6±0.9 (±6.7)	298.5±1.0 (±7.3)	2.0±0.6 † (±4.7)

* Results expressed as mean ± standard error of the mean (± S. D.).
† $0.005 > P > 0.001$.

Results

The normal values of osmolal concentrations in rabbit aqueous and plasma are presented in Table 1. The aqueous osmolal excess is statistically significant, although the magnitude is less than the values obtained by other investigators with the thermoelectric vapor-pressure method. For comparison, a review of the recent literature is presented in Table 2. The deficit of aqueous osmolality reported by Benham et al.[7] in 1937 is probably related to the use of a general anesthesia that elevated the plasma osmolality. Davson and Purvis [11] suggest that the discrepancy of their results is due to an artifact effect of the cryoscopic technique when it is used for comparison of fluids with different protein concentrations. Kinsey [17] and Roepke [23] found that no significant error was introduced by a protein concentration difference with the thermoelectric vapor-pressure method. The osmolality of a standard saline solution was determined by the present technique with and without the

TABLE 2.—*Osmolar Difference Between Aqueous and Plasma*

Reference	Species & Sample Size	Method	Aq.—Pl.	Aq.—Pl.,* mOsm./Kg. Water
Gilman & Yudkin 1933	Dog (27)	Thermoelectric of Hill	0 mM. NaCl/L.	0
Benham et al. 1937	Cat (6)	Thermoelectric of Baldes †	−1.8 mM. NaCl/L.	−3.3
Benham et al. 1938	Human (21)	Thermoelectric of Baldes	+4.0 mM. NaCl/L.	+7.4
Benham et al. 1938	Dog (14)	Thermoelectric of Baldes	+4.5 mM. NaCl/L.	+8.3
Kirwan 1938	Human (7)	Thermoelectric of Baldes	−28 mm. Hg	
Roepke & Hetherington 1940	Dog (4)	Thermoelectric of Baldes	+5.4 mM. NaCl/kg.	+10.0
Roepke & Hetherington 1940	Dog (4)	Thermoelectric of Baldes †	+3.3 mM. NaCl/kg.	+6.5
Roepke & Hetherington 1940	Rabbit (4)	Thermoelectric of Baldes †	+1.9 mM. NaCl/kg.	+3.5
Schaeffer 1950	Human (4)	Barger	Aq.>Pl., slightly	
Kinsey 1950	Rabbit (22)	Thermoelectric of Baldes	+3.0 mM. NaCl/kg.	+5.6
Davson & Purvis 1954	Rabbit	Cryoscopic	−2% of normal conc.	−5.8

* Calculated with osmotic coefficient of 1.85.
† General anesthesia utilized.

TABLE 3.—*The Effect of Paracentesis on Aqueous Osmolality*

Aqueous Osmolality, mOsm./Kg. of Water		
Right Eye *	Left Eye	O. S. — O. D.
289.1	293.0	+3.9
300.6	299.2	−1.4
285.5	290.1	+4.6
294.2	296.0	+1.8
292.5	297.8	+5.3
286.1	290.0	+3.9
Mean		+3.02 †

* Paracentesis 45 to 60 minutes before sampling.
† $0.05 > P > 0.025$.

addition of protein, and no significant deviation was found for a protein concentration difference within the normal plasma range. It is important to note that the temperature of the fluids analyzed by the cryoscopic technique is approximately 0 C, while with the vapor-pressure method it is approximately room temperature. If the osmolal concentrations of aqueous and plasma are temperature-dependent, a difference in the results by the two methods would be anticipated.

The results presented in Table 3 illustrate that ocular paracentesis 45 to 60 minutes before sampling significantly lowered the aqueous osmolal concentration. Benham et al.[8] have demonstrated a similar effect in three dogs with use of the vapor-pressure method. This decrease is attributed to the equalization of osmolal concentrations across a more permeable blood-aqueous barrier.

The results in Table 4 illustrate the effect of intraperitoneal administration of acetazolamide on the intraocular pressure of 12 rabbits during the first hour. With use of an elevation of 3 scale units or more as a criterion for a significant lowering of intraocular pressure,[3] a positive response was obtained in 5 eyes of a total of 24 (Rabbits 6, 8, and 12). These results are comparable to those of Green et al.[15] during the first 60 minutes following intravenous administration of acetazolamide, where a positive response was obtained in 10 eyes of a total of 40. Ballintyne and Maren,[2] using a slightly more stringent criterion of significance, reported 6 reactors of a total of 40 rabbits after the use of the intravenous route. Becker and Constant[6] have demonstrated that the absence of a significant pressure decrease in most cases of the so-called nonreactors was due to an increase in the outflow resistance. A decreased flow rate was present in a large majority of these cases. The presence of positive responses after intravenous or intraperitoneal administration of the drug suggests that the ocular effect of acetazolamide is not significantly altered by use of the latter route.

TABLE 4.—*Tonometry After Acetazolamide* *

Rabbit No.		Ocular Pressure (Schiots),† Scale Units				
		Control	15 Min.	30 Min.	45 Min.	60 Min.
1	O. D.	3.5	4.0	3.0	3.0	3.0
	O. S.	4.0	4.0	3.5	4.0	5.0
2	O. D.	4.5	5.5	5.0	5.0	5.0
	O. S.	5.0	5.0	7.0	6.5	6.0
3	O. D.	4.0	3.5	3.5	3.5	3.0
	O. S.	4.0	4.0	4.0	4.0	4.0
4	O. D.	7.0	7.0	7.0	7.0	7.0
	O. S.	7.0	7.5	7.0	7.0	7.0
5	O. D.	3.5	5.0	6.0	6.0	6.0
	O. S.	4.0	5.0	5.0	5.5	5.5
6	O. D.	5.0	4.0	5.0	6.0	5.0
	O. S.	4.5	6.0	7.5	5.0	6.5
7	O. D.	4.5	4.5	4.5	4.0	4.0
	O. S.	3.5	3.0	3.0	3.5	4.0
8	O. D.	3.5	4.5	7.0	6.5	6.5
	O. S.	4.0	6.0	8.0	6.5	7.0
9	O. D.	3.0	4.0	3.5	3.5	5.0
	O. S.	5.0	5.0	6.5	4.5	5.0
10	O. D.	7.0	3.5	4.0	5.5	4.0
	O. S.	7.0	5.5	5.5	6.0	5.0
11	O. D.	4.0	2.5	3.5	3.0	4.0
	O. S.	3.0	3.5	3.0	2.5	3.0
12	O. D.	4.0	6.0	7.0	4.0	4.0
	O. S.	3.5	7.0	8.0	3.0	4.5

* Single dose, 100 mg. per kilogram of body weight intraperitoneally.
† The 5.5 gm. weight was used.

The data in Table 5 illustrate that saline did not significantly alter the rabbit aqueous and plasma osmolal concentrations two and one-half hours after administration. The results in Table 6 demonstrate that acetazolamide, in comparison with saline, did have a small but significant effect on the rabbit

TABLE 5.—*The Effect of Isotonic Saline on the Osmolal Concentrations of Aqueous and Plasma* *

	mOsm./Kg. of Water †		
	Control	Saline	Difference (Contr.—Sal.)
Aqueous	299.1±1.6 (±6.6)	297.2±1.7 (±7.1)	+1.9±1.2 (±5.1)
Plasma	296.0±2.1 (±8.9)	296.8±1.2 (±5.2)	−0.8±2.1 (±8.8)
Aq.—Pl.		−1.6±1.6 (±6.9)	

* Saline 1 ml. per kilogram of body weight i. p. two and one-half hours before sampling.
† Results expressed as mean of 18 determinations ± standard error of the mean (± S. D.). Aq. diff., $0.20 > P > 0.10$; Pl. diff., $0.80 > P > 0.70$; Aq. diff. to Pl. diff., $0.30 > P > 0.25$.

TABLE 6.—*The Effect of Acetazolamide on the Osmolal Concentrations of Aqueous and Plasma* *

	mOsm./Kg. of Water †		
	Control	Acetazolamide	Difference (Contr.—Acetazolamide)
Aqueous	301.8±1.5 (±6.7)	294.9±1.0 (±4.3)	+6.9±1.3 (±5.6)
Plasma	298.2±1.6 (±6.9)	292.3±1.5 (±6.4)	+5.9±1.4 (±6.0)
Aq.—Pl.		+2.6±1.0 (±4.3)	

* Acetazolamide 100 mg. per kilogram of body weight i. p. two and one-half hours before sampling.

† Results expressed as mean of 18 determinations ± standard error of the mean (± S. D.). Aq. (acetazolamide diff. to saline diff.), $0.010 > P > 0.008$; Pl. (acetazolamide diff. to saline diff.), $P = 0.010$; Aq.—Pl. (acetazolamide diff. to saline diff.), $0.050 > P > 0.025$; Aq. diff. to Pl. diff., $0.60 > P > 0.50$.

TABLE 7.—*Effect of Saline or Acetazolamide on the Osmolal Concentrations of Aqueous and Plasma* *

	mOsm./Kg. of Water †	
	Saline	Acetazolamide
Aqueous	305.8±0.7 (±2.3)	305.0±1.2 (±4.5)
Plasma	299.7±0.8 (±2.7)	300.9±1.9 (±7.3)
Aq.—Pl.	+6.1±1.1 (±3.6)	+4.0±1.7 (±6.5)

* Saline 1 cc. per kilogram of body weight intraperitoneally one-half hour before sampling; acetazolamide 100 mg. per kilogram of body weight intraperitoneally one-half hour before sampling.

† Results expressed as mean of 11 to 15 determinations ± standard error of the mean (± S. D.). Aq. (saline to acetazolamide $0.20 > P > 0.10$; Pl. (saline to acetazolamide) $0.70 > P > 0.60$: Aq.—Pl. (saline to acetazolamide) $0.40 > P 0 > 0.30$.

aqueous and plasma osmolal concentrations two and one-half hours after administration. However, the decreases in the concentrations of the two fluids were similar. Table 7 illustrates that after one-half hour acetazolamide did not significantly alter the osmolal concentrations of the fluids, in comparison with saline. The results in Table 8 illustrate that after two hours acetazolamide significantly decreased the osmolal concentrations of the aqueous and plasma in the dog, in comparison with their normal values. Again, the alterations in composition were similar in the two fluids. A similar depression of osmolal concentration of the dog aqueous following acetazolamide is reported by Urrets-Zavalia and Remedi [27] on the basis of alterations in electrical conductivity.

While statistical analysis of the data demonstrates that the aqueous-to-plasma osmolal relationship is not significantly altered by acetazolamide administration, the limitations of the technique must be clearly kept in mind. Analysis of the data yields a standard error of the difference of means of 0.6% to 0.7% of the normal osmolal concentration. As an osmolal change of less than twice this error may well be biologically significant, it is apparent that the absence of a statistically significant alteration does not exclude the possibility of a biologically significant alteration.

TABLE 8.—*The Effect of Acetazolamide on the Osmolal Concentrations of Aqueous and Plasma in the Dog* *

	mOsm./Kg. of Water †		
	Control	Acetazolamide	Difference (Contra.—Acetazolamide)
Aqueous	301.4±2.4 (±5.9)	294.2±2.6 (±6.5)	7.2±2.5 (±6.0)
Plasma	301.4±2.7 (±6.6)	293.0±3.5 (±8.5)	8.4±3.0 (±7.3)
Aq.—Pl.	0.0±0.7 (±1.7)	1.3±1.9 (±4.6)	

* Acetazolamide 50 mg. per kilogram of body weight i. v. two hours before sampling.

† Results expressed as mean of six determinations ± standard error of the mean (± S. D.). Aq. diff., $0.02 > P > 0.01$; Pl. diff., $0.02 > P > 0.01$; Aq. diff. to Pl. diff., $0.80 > P > 0.70$.

Comment

The main evidence in support of the view that aqueous is hypertonic to the plasma across the blood-aqueous barrier is the direct experimental demonstration that the aqueous is hypertonic to plasma obtained from the large vessels or the heart. It is important to note that this interpretation assumes a uniformity of osmolal concentration between plasma in the large vessels and that in the ocular capillaries.

The interpretation that the aqueous is hypertonic to the plasma across the blood-aqueous barrier is not consonant with certain experimental observations. Within the limits of his technique, Kinsey [18] has demonstrated that there is no measurable osmolar difference between the anterior and posterior chambers. As the transfer of water across biological barriers is generally rapid, a dilution of the anterior chamber aqueous by a net transfer of water across the iris would

be expected. Friedenwald and Becker [13] have developed an argument to demonstrate that such a dilution is of negligible magnitude. However, Kinsey's analysis of posterior and anterior chamber aqueous [18] has demonstrated that small concentration differences of electrolytes across the blood-aqueous barrier are sufficient to produce a measurable net transfer of electrolytes into the anterior chamber, and it is difficult to explain why a small osmolar difference of the same order of magnitude fails to produce a detectable net transfer of water across the same barrier.

As stated above, the hypothesis of an aqueous hypertonicity across the blood-aqueous barrier is dependent on the tacit assumption of osmolal equality between the plasma in the large vessels and in the ocular capillaries. While no direct analysis of the ocular capillary plasma is available, Wirz [28] has demonstrated by direct micropuncture that the osmolal concentration of certain capillaries in the golden hamster kidney is related to the hypertonicity of the urine rather than to normal plasma osmolal values. Similarly, the plasma of the ocular capillaries might well be slightly hypertonic to the plasma in the large vessels but isotonic to the aqueous. The maintenance of this capillary plasma hypertonicity would be dependent on the integrity of the capillary wall, and so the observed decrease in the aqueous osmolality following such procedures as paracentesis would reflect a fall in the osmolal concentration of the capillary plasma. The presence of a measurable aqueous-to-plasma osmolal gradient is not necessary for net fluid transfer across the blood-aqueous barrier. If the ease of water transfer across the barrier is much greater than that of solute transfer,[12] the secretion of an osmotically active particle would be immediately followed by an associated osmotic transfer of water, with no measurable steady-state osmolal gradient across the barrier.

On the assumption of an aqueous hypertonicity across the blood-aqueous barrier, it was postulated that the increased intraocular pressure in outflow obstruction was due to the transformation of the normal osmolal gradient into its equivalent hydrostatic pressure.[1,16] However, the development of a large hydrostatic pressure by the active transport of fluid is possible without recourse to a preexisting hypertonicity of the secreted fluid. The pressure developed by the obstructed salivary gland can be cited as an example.[9]

Considerable controversy has centered about the mechanism of action of acetazolamide in reducing the aqueous flow rate. Within the limitations of the present technique, the maintenance of the normal steady-state aqueous-to-plasma osmolar relationship suggests a similar reduction in the transfer rates of the osmotically active substance and water. This is consistent with the hypothesis of isotonicity across the blood-aqueous barrier; for the rate of water transfer would be determined by the rate of active solute transfer.

Summary

The mean (plus and minus the standard error of the mean) normal osmolal values, obtained with the cryoscopic technique in 55 rabbits, are 300.6 ($\pm$0.9) mOsm. (milliosmoles) per kilogram of water for aqueous and 298.5 ($\pm$1.0) mOsm. per kilogram of water for plasma. The aqueous excess is statistically significant. Paracentesis of the eye is associated with a fall in aqueous osmolal concentration.

Intraperitoneal administration of acetazolamide lowered the intraocular pressure in 5 eyes of a total of 24. The osmolal concentrations of aqueous and plasma are not significantly altered one-half hour after administration of the drug, but they are significantly decreased after two and one-half hours. The decrease in concentration is similar for the two fluids. Two hours after intravenous injection of the drug into dogs, a significant decrease is obtained in the aqueous and plasma. Again, the decrease in the concentration of the two fluids is similar. The standard error of the difference of means in these comparisons is 0.6% to

0.7% of the normal osmolal concentration.

The concept of an aqueous hypertonicity across the blood-aqueous barrier is discussed. The validity of the basic assumption that the osmolal concentration of the plasma in the ocular capillaries is equal to that of the plasma in the main vessels is questioned. Isotonicity of the fluids across the blood-aqueous barrier is suggested as an alternate possibility.

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Punch Cards for Motility Records

A Preliminary Report

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Anyone who has attempted to analyze the data from a series of motility records is painfully aware of what a bafflingly difficult job it is. Yet some of us cling to the belief that it is only by such analysis that we can learn the value of various types of treatment.

For a number of years the use of punch cards has seemed in theory to be the logical solution to this problem, but I now find that this is by no means an easy solution. Thus far I have been able to learn of only two attempts to use punch cards for motility records: a short-lived project by Hermann Burian a number of years ago in Hanover, N. H., and a presently continuing one by Lloyd Morgan, in Toronto. As no report of either of these has yet been published, I feel justified in recording my experience in a preliminary report, in the hope that it will induce others to use punch-card methods. Possibly this report will save them time and effort.

In approaching this project, two closely related decisions must be made: (1) what type of card to use and (2) what data should be punched in the cards. As each has a direct bearing on the other, it is difficult to say which comes first.

After considerable study, I decided that the McBee Keysort cards would be the best for the average office or muscle clinic, which has up to a few thousand records, for the following reasons. 1. No expensive equipment is necessary for punching the cards because this is done with a simple hand punch (Fig. 1), one for which no training is required. 2. In most instances this punching can be done directly from the records, thus eliminating an intermediate work sheet. 3. The sorting is done with extremely simple equipment (Fig. 2). Anyone familiar with the motility records can quickly learn to punch and sort these cards.

Having settled the type card to be used, we had to decide what data we wanted to

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Fig. 1.—Hand punching. (From the McBee Company.)

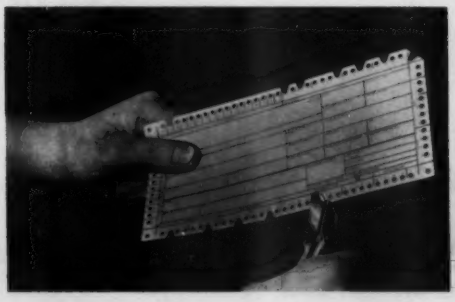
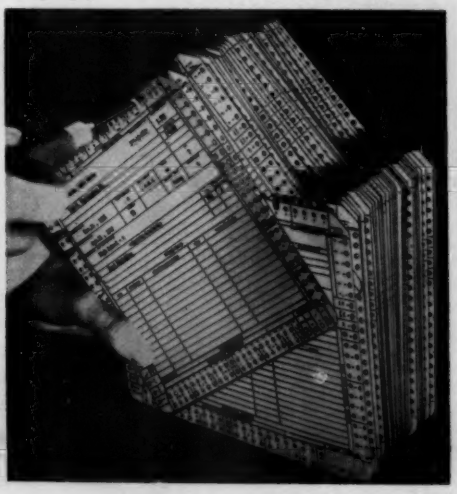


Fig. 2.—Sorting punch cards. (From the McBee Company.)



include.* In the beginning we put down everything we could possibly imagine ever wanting. Next we tried to see how much we could get on a single large card (8×10.5 in., with a double row of punches all the way around), but we found that we had far too much. After innumerable sessions we finally trimmed the material down so that it would fit on a single card, but the pruning had been so severe that the result was almost worthless.

Extending the data from one case onto more than one card creates serious complications. These cards must be tied together by means of a numerical code (see below) which uses many valuable holes. Comparing data on the different cards complicates the sorting. The original expense is increased materially because of the cost of additional engravings, used in printing different cards.

There are, however, at least three advantages to using more than one card. 1. Many more data can be included. 2. Smaller cards may be possible (as in our case), making them easier to store and handle. 3. Much more important, they may make for much more flexibility.

As we finally worked it out, we gained flexibility by using three cards, 5⅛×7½ in., five holes to the inch. Card 1 (Fig. 3), printed in brown, records the history and the original examination. Once this first card is completed, it should not be changed by subsequent visits. Card 2 (Fig. 4), printed in blue, shows the treatment ending after surgery. Once completed, this card also should not need to be changed. If there is a second operation, a second No. 2 card should cover the treatment between operations and the second surgical procedure. Similarly with additional operations, a new No. 2 card would be added for each.

Card 3 (Fig. 5), printed in green, covers the postoperative treatment and the final summary. If subsequent visits change any of these data, it is only this last card that needs to be changed. A fourth card con-

* Dr. Philip Knapp and Miss Nancy Capobianco helped in this work.

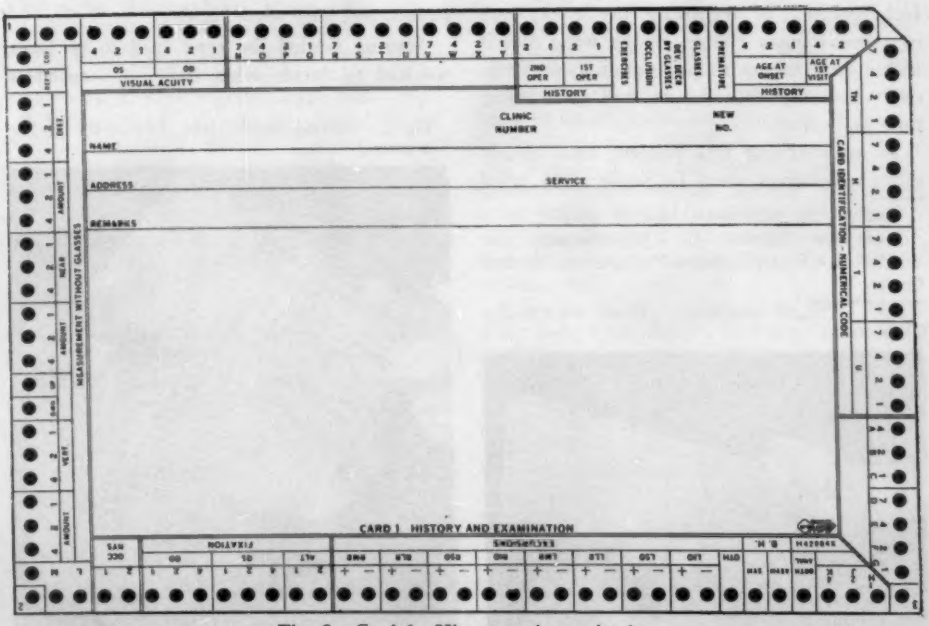


Fig. 3.—Card 1. History and examination.

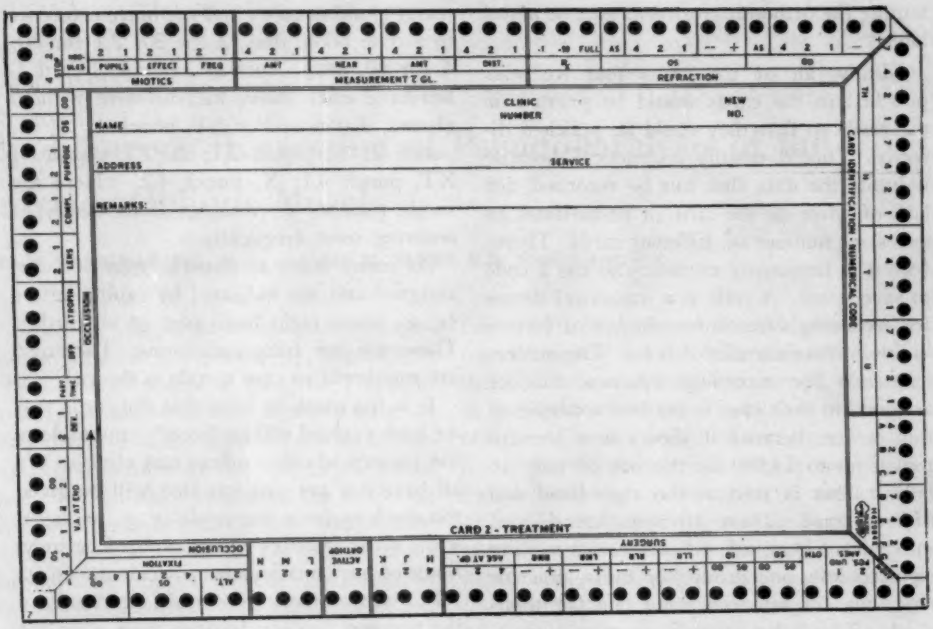


Fig. 4.—Card 2. Treatment.

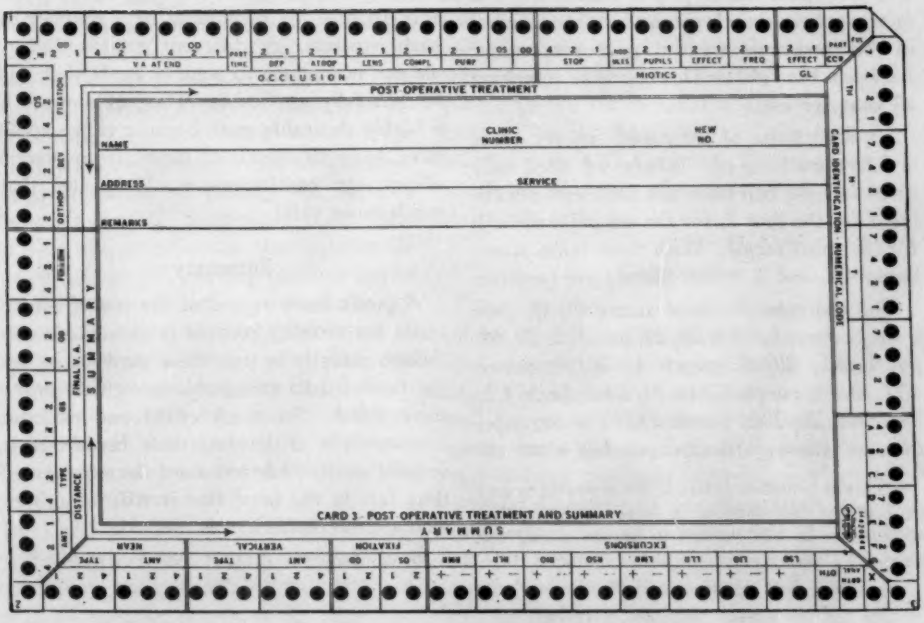


Fig. 5.—Card 3. Postoperative treatment and summary.

taining the orthoptic treatment may be added later.†

Ideally, all of the items that we wish punched in the cards would be printed on the cards so that they could be punched directly. This is usually impractical, because it limits the data that can be recorded, for lack of space on the card, or necessitates an excessive number of different cards. Therefore it is frequently necessary to use a code to save space. A code is a numerical device for recording a maximum number of factors in a minimum number of holes. The numerical code for recording the new number assigned to each case is the best example of this device, because it shows how we can punch up to 14,999 by the use of only 16 holes. This is seen at the right-hand end of each card. These 16 holes are divided into four groups of 4 holes each: reading right to left, one group for units, one for tens, one for hundreds, and one for thousands. The holes in each group are numbered 7,4,2,1. Any digits of 7,4,2, or 1, of the case number, are punched directly. If 3 is wanted, punch 2,1; if 5 is needed, punch 4,1, etc., and for 9 punch 7 and 2. The same applies to each group, but, in addition, in the thousands we can go beyond nine: 7,2,1 for 10; 7,4 for 11, etc., up to punching all four for 14.

In other parts of the cards, smaller codes are frequently used. Where we need only three factors, two holes are sufficient, punching 1 for the first 2, for the second, and both for the third factor. With three holes, numbered 4,2, and 1, seven factors are possible.

For example, if visual acuity O. D. (see Card 1, upper left) is 20/20, punch 2; 20/30, punch 2,1; 20/40, punch 4; 20/50, punch 4,1; 20/70, punch 4,2,1; 20/200, punch 4,2; less than 20/200, punch 1. (The arrangement of these particular punches is an attempt to aid memory and minimize reference to a code book, thus, 2 for 20; 2,1 for 30; 4 for 40, etc.) Another example (Card 1, left-hand end) shows measurement without glasses, distance: For ST, punch 1; S(T), punch 2; S, punch 2,1; X(T), punch 4; XT, punch 4,1; X, punch 4,2. (Here the single punches were assigned to the types ocurring most frequently.)

As many holes as possible were left unassigned and are indicated by capital letters (e. g., lower right hand part of all cards). These are for future additions. They also are numbered in case a code is desired.

It is too much to hope that the cards that we have evolved will be directly applicable to the records in other offices and clinics. We all have our pet projects that will be given too much space on the cards (e. g., miotics), while other features will be omitted entirely. Some of our omissions were accidental (e. g., NPC) while others were made reluctantly in the pruning process, because even when we finally expanded to three cards the data still had to be restricted fairly rigidly. The unassigned holes in the cards will provide for minor changes or additions, but it will probably require the combining of a number of such projects, by different groups, before we can even hope to achieve cards that will be generally applicable. This, of course, is a highly desirable goal, because if we could have many thousands of cards, from several clinics, our conclusions would be just that much more valid.

Summary

A preliminary report of the use of punch cards for motility records is presented. Although actually in use, these cards have not yet been used extensively enough to prove their worth. So much effort and expense was involved in devising these cards that it seemed worth while to record the experience, thus far, in the hope that it will aid others who are interested in this method.

30 W. 59th St. (19).

† Since it is neither practical nor desirable to give here all the data included in these cards, samples, with the code, will be sent to anyone asking for them.

Case Reports

Spontaneous Regression of Pseudoparalysis of the Inferior Oblique Muscle

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Since the "superior oblique sheath syndrome" was first reported by Brown,[1] in 1950, it has become a recognized clinical entity. In this condition a short anterior tendon sheath of the superior oblique muscle restricts elevation of the eye in the nasal field. Brown has established the following diagnostic criteria: paralysis of the inferior oblique muscle, little or no overaction of the superior oblique muscle, depression of the eye on adduction, and limitation of the adducted eye to passive elevation. Girard[2] has pointed out that other structural changes may prevent the normal action of the inferior oblique muscle. He describes four types of such changes and has suggested the term "pseudoparalysis of the inferior oblique muscle." Type I he considers congenital retraction of the tendon sheath of the ipsilateral superior oblique ("superior oblique sheath syndrome" of Brown); Type II, retraction of the tendon sheath produced as a complication of tucking the superior oblique; Type III, anomalous check ligaments on the insertion of the inferior oblique, and Type IV, swelling on the superior oblique tendon, restricting passage through the trochlea. Since surgical exploration of many of these conditions is contraindicated or impossible, it would appear that the term pseudoparalysis of the inferior oblique muscle should be used until the more definitive diagnosis can be made by studying the surgical anatomy.

In 1949, one of us (F. D. C.) saw a 3-year-old white boy with a history of an intermittent vertical strabismus since infancy. He was found to hold his head turned slightly to the left, with chin elevated. There was complete lack of motion in the field of action of the left inferior oblique. He was seen again at ages 5 and 6 years. At these visits, there was still complete absence of elevation in adduction O. S. The left superior oblique functioned normally; there were no abnormal torsional movements noted with the eye adducted, and movements and fusion were normal in all other fields. An investigation of the sheath of the left superior oblique was suggested but was not done.

About six months later the child was seen again. The anomalous head position had disappeared, and there was now complete recovery of motion in the field of the left inferior oblique muscle. He was orthophoric in the six cardinal fields of gaze at distance and displayed a concomitant esophoria of 4 △ for near. Fusion seemed stable in all fields when examined by the red-green test.

Comment

The spontaneous establishment of full ocular motility makes speculation regarding the etiology of the original lesion interesting. The absence of secondary contracture and the presence of normal torsional movements make the diagnosis of primary inferior oblique paralysis unlikely, and so the original diagnosis of pseudoparalysis seems justified. Lysis of a congenital retraction of the superior oblique sheath or of an anomalous check ligament at the insertion of the inferior oblique seems quite im-

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probable. Although entirely speculative, it seems more likely that a restriction to the free passage of the superior oblique tendon through the trochlea may have lessened, thus allowing for full excursions of the inferior oblique muscle.

Summary

A case of pseudoparalysis of the inferior oblique muscle that disappeared spontaneously is presented. Speculation as to the pathogenesis is given.

1605 22d St. (8).

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Papilledema Complicating Retinitis Pigmentosa

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The occurrence of carcinoma of the breast with cranial metastases in a patient with advanced retinitis pigmentosa afforded an opportunity to observe the behavior of the affected retinas in the presence of increased intracranial pressure.

Report of Case

A 47-year-old white married woman was first seen in October, 1952. She complained of a lump in her right breast noted one year previously and undergoing progressive enlargement. On Oct. 26, 1952, following preliminary biopsy, a right radical mastectomy was performed. Pathologic examination revealed an infiltrating duct-cell carcinoma with metastasis to axillary lymph nodes. One month postoperatively she was given five x-ray treatments, 1800 r to the right supraclavicular area and 1500 r to the right axilla.

The patient did well until July, 1954, at which time she developed a lump in the right infraclavicular area. Radiologic survey revealed widening of the mediastinum, questionable infiltration of the left lung, and osteolytic metastasis involving the skull and possibly the spine and pelvis. Biopsy of the nodule in the left infraclavicular region revealed metastatic adenocarcinoma. On July 26, 1954, bilateral oopherectomy with right salpingectomy and appendectomy was performed.

After the latter procedure the patient's course was satisfactory. There was no evidence of further tumor spread. Chest x-ray revealed a disappearance of the mediastinal widening previously noted.

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From the Department of Ophthalmology (Dr. Donin) and the Department of Surgery (Dr. Crowley), the Southern California Permanente Medical Group.

In June, 1955, a repeated radiologic survey revealed an increase in osteolytic metastases. The patient was given testosterone propionate, 150 mg. twice weekly. In November, 1955, she complained of severe pain in the left upper arm. X-ray examination earlier had revealed the left humerus as one of the sites of involvement by metastatic tumor. She was given a second course of x-ray therapy to this site, with relief of pain.

In February, 1956, the patient was seen in the eye department for routine refraction. She stated that she had been night blind all of her life. She had not been aware of serious visual difficulty until the age of 40 years. For the past few years, this blurring of vision had been getting progressively worse. She stated that she was an only child and that there was no family history of consanguinity or visual difficulty. Two teen-aged sons examined shortly thereafter revealed no evidence of ocular disease. Eye examination was as follows: Vision without correction was 20/60 in the right eye and 20/40 in the left eye. Externally, the eyes appeared normal. The pupils were round, regular, and equal and reacted promptly to light and in convergence. Ocular rotations were normal. Intraocular tension was 20 mm. O. U. (Schiøtz). Visual fields were markedly constricted; a residual central field measuring approximately 5 degrees was present in each eye. Following pupillary dilatation, a tiny posterior polar opacity was noted in each lens. Ocular media were otherwise clear. Ophthalmoscopy revealed waxy optic discs. The retinal arterioles, and to a smaller degree the retinal veins, were attenuated. There were extensive pigment deposits in the retinal peripheries, primarily along the course of the retinal veins. The picture was typically that of retinitis pig-

mentosa. Refraction revealed a small astigmatic error. Corrective lenses improved the visual acuity to 20/50 in the right eye and to 20/30 in the left eye.

In March, 1956, the patient complained of recurring pains in her arms and legs. In addition, she had noted the onset of headache, diminished vision, loss of weight, nausea, and vomiting. X-ray examination revealed a further increase in bony lesions involving the skull, spine, pelvis, and both upper and lower extremities. On March 30, 1956, following a preliminary course of cortisone therapy for one week, bilateral adrenalectomy was performed. The postoperative course was satisfactory, and gradual reduction of cortisone therapy was attempted. When a daily dosage of 37.5 mg. was reached, there was a sudden marked deterioration of her condition; she developed severe retro-orbital headaches, nausea and vomiting, and further blurring of vision.

Ocular examination on April 7, 1956, revealed that the vision in both eyes had been reduced to bare light perception. After pupillary dilatation, ophthalmoscopy revealed swelling of both optic discs. The disc margins were well defined, but centrally there was elevation measuring 1½ to 2 D. Each optic disc was surrounded by a rosette of flame-shaped hemorrhages. Both retinal arteriolar and venous trees, though narrowed, were dilated in comparison with their appearance on previous examination.

The patient's sudden deterioration, including the onset of almost complete blindness, was attributed to the reduction in the maintenance dose of cortisone. Earlier improvement prior to and following bilateral adrenalectomy took place while the patient had been taking 300 mg. of cortisone daily. Such large dosage is known to cause suppression of the adrenocorticotropic and probably other pituitary hormonal secretions. When the dosage of cortisone was reduced to 37.5 mg. daily, it was postulated, the removal of this inhibiting effect on the pituitary gland resulted in markedly increased pituitary activity, which in turn stimulated a rapid increase in tumor growth. In an attempt to reverse this phenomenon, the patient was again given 300 mg. of cortisone daily. Her general condition improved promptly and strikingly. Repeated eye examinations were carried out during the month that followed. The patient reported a slight improvement in vision, though this was not measurable. The degree of papilledema varied; the circumpapillary hemorrhages absorbed and then recurred. By May 21, 1956, all the hemorrhages had absorbed completely but measurable disc elevation of 1 D. remained in each eye.

In June, 1956, the patient was discharged home, taking 200 mg. of cortisone daily. Eye examination on July 3, 1956, revealed that the vision had improved to 20/50 in the right eye and to 20/30 in the left eye. Visual fields had returned to their original configuration. The optic discs were again flat, and the entire ophthalmoscopic picture had reverted to the original condition.

The patient continued to do well. Except for recurring subcutaneous abscesses in the right arm, she was asymptomatic. On Aug. 27, 1956, following a comfortable and uneventful day, she was found dead in bed. Necropsy revealed the cause of death to be acute hemorrhagic pancreatitis. In addition, large areas of anaplastic metastatic tumor tissue were found in the liver, the skeletal system, the dura, and the brain. Over one-half of the left occipital lobe was replaced by tumor. The eyes were not obtained for pathologic examination.

Comment

There would seem to be little doubt that this patient had true papilledema. Though the appearance of the discs was not entirely typical of papilledema, there was measurable elevation accompanied by retinal venous engorgement and circumpapillary hemorrhages. The development of this retinal picture coincided with the onset of severe headache. As a final piece of corroborative evidence, cranial metastases were demonstrated at necropsy.

The condition of the optic nerve in retinitis pigmentosa is commented on by the authors of "Ophthalmic Pathology."[1] They noted that in many pathologic studies the optic nerve has been described as atrophic but that in four of five cases examined by Cogan it was normal. Cogan was unable to account for the waxy appearance ophthalmoscopically. If an optic nerve is completely atrophic, with destruction of nerve fibers, disappearance of capillaries between fiber bundles, and glial and fibrotic proliferation, it might be expected that such a nerve would be unable to demonstrate papilledema in the presence of increased intracranial pressure. On the other hand, if the optic nerve is entirely normal, one might expect a typical picture of papilledema. In this case we found edema limited to the central part of the optic nerve. This would suggest that, even in the presence of advanced visual field loss, there was sufficient normal optic nerve structure remaining to undergo ophthalmoscopically appreciable edema.

The complete return of former visual function following the subsidence of the papilledema demonstrated an apparent resistance of the remaining macular fibers to destruction by the superimposed circulatory disturbance.

Southern Permanente Medical Group.

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Annual Reviews

The Lens and Vitreous

WILLIAM COUNCILMAN OWENS, M.D., Easton, Pa.

In this review of the literature on the lens and vitreous published during 1957, no attempt has been made to mention every article that has appeared. Instead, only those reports that have interested me most have been included. The general outline of topics is the same as in the summary of the literature for the previous year.[1]

Surgery of the Lens

Preoperative Complications.—At a conference held by the New York Society for Clinical Ophthalmology on the subject of cataract,[2] all of the participants agreed that intracapsular extraction of the cataract was indicated when high myopia, inactive uveitis, or posterior synechias were present as preoperative complications. They also felt that an intracapsular extraction should be done when the cataract was atopic in origin. When the cataract is associated with phacogenic glaucoma, its prompt removal by the intracapsular technique is advocated by Hopkins.[3] The intracapsular technique of extraction was also advocated in cases of cataract associated with retinitis pigmentosa. In this condition Alberth[4] found that an only moderate lens opacity will produce a severe visual loss when the field is restricted, and he therefore recommends early operation. Stankovié and Kecmanovié[5] recommend the intracapsular technique when the cataract is complicated with megalocornea. They believe that the unfavorable prognosis previously associated with these cases is unwarranted.

Choyce[6] recommended the immediate extraction of the lens if it entered the anterior chamber in cases of Marfan's syndrome; otherwise glaucoma might result if the lens became trapped by the iris sphincter. Hilding[7] reported the case of a 2½-year-old child with bilateral complete dislocations of the lens. In each eye, glaucoma occurred when the freely moving lens became incarcerated in the pupil. In both his cases successful intracapsular extractions were performed.

The lens has again been incriminated in the occurrence of malignant glaucoma. Birge[8] believes that eyes likely to develop malignant glaucoma can be detected before filtering operations are performed. He feels such eyes have microphthalmos, microcornea, early cataractous changes, or advanced acquired myopia in association with chronic narrow-angle glaucoma not controlled by medication. In such eyes, he states, the operation of choice is an extraction of the lens combined with a filtering operation. Ourgaud and Bérard[9] recommended the reduction of the intraocular tension before filtering operation and the use of mydriatics following the filtering operation in an effort to prevent malignant glaucoma. However, if it occurs, they stated, immediate extraction of the lens should be performed. Four cases of malignant glaucoma following antiglaucomatous operations were described, and lens extraction was advocated as the best treatment by Rougier, Chavanne, and Paufique.[10]

Instruments.—The use of a special microscope for ocular surgery has been advocated by Barraquer.[11] The focus of the microscope he used can be controlled with a foot pedal.

In addition, a slit lamp has been mounted on an arm so that it can be used when necessary in operations such as lamellar keratoplasty. A different method of cataract

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extraction was described by Unsworth.[12] He used a special forceps which consisted essentially of a lens spoon for its posterior blade and a lens loop for its anterior blade. After direct rupture of the zonules, this special forceps was slipped down over the superior equator of the lens, one blade in front and one behind the lens, which was then extracted. Scheie[13] has produced a corneoscleral scissors with a heavy shank and blunt tips for increased safety in enlarging the cataract section.

Anesthesia.—Stringham[14] has written an excellent article on pediatric anesthesia and gives the technique he uses. Patients over 5 months of age are given rectal premedication with pentobarbital (6.5 mg. per kilogram). In children over 5 years of age this is supplemented with an opiate and a belladonna drug. Induction is accomplished with cyclopropane and ether, and the anesthesia is maintained with ether by the endotracheal route. Because of the extensive fluid loss by way of the lungs in infants, early adequate fluid replacement is necessary, and intravenously administered 5% dextrose in water is therefore used in most operative cases. He points out that in infants it is also most important to replace any significant blood loss.

More surgeons are recommending the use of chlorpromazine. Harley and Mishler[15] tested the effect of administration of chlorpromazine on the occurrence of nausea and vomiting during and after cataract operations. In 100 control cases the following preoperative medication was used: sodium pentobarbital (Nembutal), 100 mg. the evening before surgery; nothing by mouth for four hours before opertion; sodium pentobarbital, 100 mg., given four hours preoperatively and repeated one hour preoperatively, and, finally, meperdine (Demerol), 50 to 100 mg. according to weight and age, and dimenhydrinate (Dramamine), 50 mg. one-half hour preoperatively. In 100 other test cases chlorpromazine, 25 mg., was given orally one-half hour before surgery in addition to the preoperative medication given to the control cases. Chlorpromazine, 25 mg., was also given parenterally immediately postoperatively and again as frequently as every three hours for nausea and vomiting. From this study they found chlorpromazine to be helpful in reducing the incidence of nausea from 27% to 19% and that of vomiting from 18% to 8%. They suggested that the routine use of chlorpromazine postoperatively (25 mg. every six hours) for 48 hours may further reduce the incidence of postoperative nausea and vomiting. Agarwal, Gupta, and Malik[16] came to essentially the same conclusions in a study of the use of pentobarbital and chlorpromazine in 95 cataract operations.

Most authors have advocated methods to obtain maximum hypotony during surgery. Some have advocated use of acetazolamide (Diamox) both before surgery and at the time of surgery if the iris-lens diaphragm bulges forward when the eye is opened. De Saint-Martin[17] obtained hypotony by the use of hyaluronidase in the retrobulbar injection. He believes that the softness of the eye does not interfere with making the section, placing the sutures, or extracting the lens.

Technique.—Some modifications and changes of the type of suture have been described. Buxeda[18] used a double-ended suture, placing one needle from the limbal groove through the sclera and the other needle from the limbal groove through the cornea. He believes that this obviates the difficulty he sometimes encounters when the suture is placed too deeply. Barraquer Moner[19] advocated placing nonabsorbable surgical (silk) sutures beneath a conjunctival flap. When this was done, the silk sutures remained indefinitely in one-quarter of the cases but in most "the stitches were spontaneously eliminated between 20 and 30 days after the operation."

A comparison[20] of the results of the round-pupil versus the iridectomy technique of cataract extraction was made in a study of 14 cases with bilateral aphakia, one eye having a round-pupil and the other eye, a key-

hole iridectomy. No noticeable subjective or objective differences were noted in the results of the two types of operative procedure.

It was surprising to find two papers supporting the expression of cataracts as opposed to extraction. These give new life to the Smith method, which of late years has been lying dormant. Hruby [21] described his own modification of the Smith technique, which he feels gives better results than any method of extraction of cataract. Nirankari and Maudgal [22] advocate their modification of the Smith technique, in which pressure is applied above on the upper pole of the lens at the same time that pressure is applied to the zonule below.

Lister [23] advocated the use of air in the anterior chamber following cataract extraction.

Rumbaur [24] described a technique for removing a dislocated lens from the vitreous by first bringing the dislocated lens into its normal position with a diathermy needle inserted into the lens under direct observation.

Intraocular Lenticular Substitutes

The interest in intraocular lenticular substitutes continues. Epstein [25] reported on the results obtained in 84 cases in which the Ridley lens was implanted. In 12 there was failure. The failure was due to corneal degeneration in four cases and to luxation of the acrylic lens into the anterior chamber in five cases. These five cases had cataracts due to trauma. In two cases with intracapsular extraction the lenticulus slipped into the lower portion of the posterior chamber. In the remaining case failure was due to iridocyclitis and glaucoma. In many of the cases, Epstein reported, there was a significant, but not incapacitating, slipping of the lenticulus toward the 6 o'clock position of the posterior chamber. A formidable number of secondary operations were required in the 84 cases reported. Posterior needlings with insertion of the knife into the vitreous from a point 5 mm. posterior to the temporal limbus were required 24 times, and anterior needlings were used 15 times, giving a total of 39 needlings in the 84 cases. In six cases there were hyphemas large enough to fill one-half of the anterior chamber. In most of the cases compound myopia astigmatism was found. Epstein recommends injection into the anterior chamber of equal parts of hydrocortisone acetate and the hydrocortisone free alcohol. He stresses the need for dressings twice a day for the first four or five postoperative days.

Reese and Hamdi [26] gave the results in 115 cases operated upon by the Ridley technique of implanting an acrylic lenticulus after cataract extraction. In only four cases was it necessary to remove the implant. In 5% glaucoma developed, and in 5% an exudative pupillary membrane developed requiring incision with a needle knife. One of the most distressing complications was postoperative uveitis, causing hypopyon in four cases in this series. The authors state that all cases had a certain amount of exudation into the anterior chamber and redistribution of pigment that frequently resulted in heterochromia. Their visual results were good, although they expressed the belief that "direct vision is better in the modern conventional cases but field of vision, orientation, and perspective are better in the Ridley cases."

F. Ridley [27] wrote an excellent paper in which he described the procedure for manufacture, cleaning, sterilizing, and using intraocular acrylic implants. He feels that adhering to the precautions he outlined will remove many of the disadvantages, especially the tendency to produce inflammation, that have hitherto been associated with the use of acrylic implants in ophthalmology. According to his instruction cleaning of the implants should be done with sodium lauryl sulfate, 0.1% solution, at 40 C for five minutes, followed by washing with distilled water. The lenticulus should be sterilized with sodium hydroxide, 10% solution, at 30 C for 60 minutes, and it should be stored in 0.1% sodium hydroxide solution in special polyethylene containers. At the time of using the implant, the storing solution should

be poured off and 0.5% solution of sodium bicarbonate should be added to neutralize the adherent sodium hydroxide solution. He laid emphasis upon the use of dry forceps, not contaminated with any detergent or other antiseptic, and upon the avoidance of contamination with talc or other glove powder. All washing of the anterior chamber should be done with a glass syringe and metal cannula, with avoidance of any apparatus consisting of rubber and metal tubing.

However, H. Ridley himself [28] stresses the two main complications—reactionary iritis and late dislocation of the lenticulus—in cases where the lenticulus is placed behind the iris. He therefore describes his modification of an implant, supported by three legs, to be placed into the anterior chamber. King and Skeehan [29] introduced acrylic lenticuli into the anterior chamber of two monkeys and three cats. In one of the cats severe iritis occurred clinically. Eighteen months after the operation the eyes of the two monkeys and one cat were examined histologically. Although no severe inflammation was present, mild iritis and cyclitis were found in all.

Contact Lenses

The main indication for the use of intraocular lenticular substitutes has been in young persons with monocular cataract, to overcome the high anisometropia that results from monocular aphakia. Another, and perhaps simpler, way of handling the problem of monocular aphakia is by the use of contact lenses. Goar [30] reports on 63 cases fitted with contact lenses for correcting the refractive error of monocular aphakia. In only four was the use of the contact lens abandoned. In 13 cases operation was subsequently performed on the remaining eye, and so binocular aphakia resulted. However, it was most remarkable that of these 13 cases, 10 chose to continue the use of contact lenses, having a new lens fitted for the eye more recently operated upon. Goar warns against the danger of lens-induced glaucoma if a cataract is allowed to go to hypermaturity, while one is waiting for the drop in vision in the better eye. He feels that cataract extraction and the use of a contact lens for the resulting anisometropia is the answer.

McLean [2] also pointed out the dangers of secondary glaucoma and lens-induced uveitis which occurs in unoperated-on monocular cataract, and he stated that after successful removal of the monocular cataract most patients had a good chance of binocular vision when contact lenses were used.

Levitt [31] described the successful use of a contact lens in a 7-year-old boy to correct the refractive error of monocular aphakia, and Lock [32] used a contact lens successfully in a 22-year-old seaman with monocular aphakia.

Verhoeff [33] suggested that, in all cases with anomalous projection and unilateral cataract, the cataract should be removed as soon as the corrected visual acuity in the affected eye would be improved by the operation. In addition, he stated that such patients should wear the best correcting spectacle lens for each eye. These conclusions were reached as a result of a remarkable case of latent nystagmus with heterochromic uveitis and cataract in the left eye and esotropic amblyopia of 20/50 visual acuity in the right eye. Following successful intracapsular cataract extraction, corrected vision of 20/20 was obtained in the left eye. However, when a blurring +10.00 sphere was placed in front of the strabismic right eye, latent nystagmus reduced the visual acuity of the left eye. Therefore, the spectacle which gave the strabismic right eye the best visual acuity was prescribed and was successfully worn with the aphakic correction for the left eye.

Aphakic Refraction

Stimson [34] wrote about the problem of refraction for the aphakic patient. He advocated the immediate selection of the final permanent spectacle frame postoperatively. A temporary lens is then fitted into this permanent frame. The final vertex distance,

height, and inclination of the frame can then be established and maintained constant. With the frame factors established, all subsequent refractions should be made over the temporary lenses with the final frame in place on the patient's face. He has found that straight-top bifocals are the most satisfactory shape in aphakic correction.

Postoperative Complications

A symposium on postoperative cataract complications was held by the American Academy of Ophthalmology and Otolaryngology. Postoperative infection still remains one of the most formidable complications. Hogan [35] recommends prophylaxis locally with a sulfonamide, a preparation of polymyxin B and bacitracin (Polysporin) or an ointment containing bacitracin, neomycin, and polymyxin B (Neosporin) applied to the lid margins two or three times a day for a week prior to surgery and at the daily dressings of the eye postoperatively. There is some difference of opinion on the use of systemic prophylaxis. It is agreed, however, that systemic use of penicillin should be avoided because of the increasing resistance of staphylococci and of the increasing incidence of serious allergic reactions in patients receiving it. The preparation of the patient at the time of surgery should be with pHisoderm, a preparation containing 3% hexachlorophene, followed by 3.5% iodine or 1:1000 tincture of benzalkonium (Zephiran) chloride. Nonsharp instruments should be sterilized in an autoclave, and sharp instruments should be individually packaged and sterilized with dry air.

If infection occurs, Hogan [35] states, a Staphylococcus should be suspected, but cultures should be taken immediately and the eye left unbandaged behind a protective screen. Systemic therapy with sulfadiazine, 3 to 4 gm. a day by mouth, combined with chloramphenicol (Chloromycetin), tetracycline (Acromycin), or erythromycin in dosages of 2 to 3 gm. a day should be given. Local treatment should consist of subconjunctival injection every 24 to 48 hours of penicillin plus streptomycin, as described by Pearlman,[36] and Neosporin ointment every two hours. In rapidly progressive cases the injection of 5000 units of penicillin into the anterior chamber or vitreous is warranted. When the results of culture have been determined, the antibiotics and chemotherapeutic agents can be adjusted to the organism and its sensitivity.

Three cases of panophthalmitis caused by Pseudomonas aeruginosa (pyocyanea) were described,[37] and prophylaxis postoperatively, by the use of polymyxin and neomycin solution and subconjunctival injection of neomycin, was advocated. A case was reported of smoldering uveitis occurring in an eye one month after cataract extraction.[38] After intensive antibiotic and steroid therapy failed to control the inflammation, the eye was enucleated. In the histologic sections a fungus was found.

For incarceration of the iris into the wound, McLean [39] advocated the use of a combination of miotics and adrenergic drugs. Weisel and Swan [40] believe that pupillary block is an important factor in the production of a shallow anterior chamber following cataract extraction. They found increased convexity of the peripheral iris and herniation of the vitreous into the pupillary area to be a prominent feature. They recommend a complete dilatation of the pupil as treatment. They advocate the combination of scopolamine or atropine with an iris dilator of the sympathomimetic group. When mydriatics, acetazolamide, and air infection have failed to restore the anterior chamber postoperatively, Bellows [2] found that incision of the anterior face of the vitreous promptly re-formed the chamber.

When vitreous has been lost at operation, Maumenee [41] advocated the use of four or five corneoscleral sutures, injection of air into the anterior chamber, and freeing the wound of vitreous, both from the outside by cutting the prolapsed vitreous with scissors and from the inside with a sweeping motion of the iris reposition. For epithelial downgrowth he recommended biopsy and surgical

removal, and for iris cyst, aspiration and diathermy or excision. Long and Tyner [42] reported three cases in which an epithelial downgrowth was removed surgically by forceps and curettage followed by application of 70% ethyl alcohol to the cornea. However, in only one case was a good result obtained. In the other two, a severe postoperative uveitis occurred; in one sympathetic ophthalmia resulted, necessitating enucleation. Vannas [43] is pessimistic about all treatment of epithelial downgrowth and advises prophylaxis.

Stocker [44] found that carbazochrome (Adrenosem) salicylate was of no use in preventing the occurrence of postoperative hyphemia. Likewise, Vail [45] found the administration of acetazolamide to be ineffective. Acetazolamide was used to determine whether the occurrence of postoperative hyphemia was related to the return of intraocular pressure postoperatively. It was thought that acetazolamide might reduce the incidence of hyphemia by keeping the intraocular pressure reduced during the postoperative period. Dunnington's [46] experiments in animals, however, suggested that return of intraocular pressure did not open the wound and thereby cause hyphemia. His experiments showed that marked increase in the internal pressure did not produce hyphemia after operation but that the slightest externally applied pressure was associated almost inevitably with the occurrence of hyphemia.

Tonography and gonioscopy performed after cataract extraction have shown a period of hyposecretion of aqueous lasting from 6 weeks to more than 15 months after operation. Miller, Keskey, and Becker [47] found these results in a review of 139 eyes studied before and after cataract surgery. The decreased rate of secretion may mask the danger of subsequent glaucoma unless the cases are reevaluated postoperatively at frequent intervals. They found that peripheral anterior synechias are formed even in uncomplicated cataract extractions. The reduction in outflow and the extent of peripheral anterior synechias were correlated with the amount of lens material left in the eye and the severity of postoperative hyphemia. Rupture of the lens capsule at the time of surgery was found to be the most important offender in producing postoperative glaucoma—30% of the cases resulting in glaucoma and accounting for two-thirds of all the secondary glaucoma encountered in their series. Lee and Trotter [48] also found that the facility of aqueous outflow usually diminished after cataract extraction. They recommended early gonioscopy and miotic therapy following postoperative flat anterior chamber.

Stokoe [49] described an unusual postoperative complication. A Soemmering ring became spontaneously dislocated into the anterior chamber, from which it was successfully removed by operation.

Clinical Observations of the Lens

Congenital Malformations.—Armaly [50] pointed out the importance of bilateral congenital cataracts in the differential diagnosis and prognosis of chondrodystrophia calcificans congenita punctata. Infants affected with this condition are short-limb dwarfs with discrete foci of calcification in the regions of enchondral ossification. The cataracts seen are usually of the dense nuclear type with peripheral radiating spokes. The presence of cataracts rules out the milder congenital anomalies of bone growth, which have a good prognosis.

Joseph [51] reported the occurrence of cataract in two sisters and supposed the defect to be of recessive autosomal inheritance.

Cataracts Associated with Skin Disorders. Rud [52] described three cases of Werner's syndrome with bilateral cataracts and atrophic skin and subcutaneous lesions. Two of the cases had keratitis, but the author questioned whether the corneal lesion was a part of the clinical syndrome. Charleux and Paufique [53] pointed out that the presence of associated skin lesions should be considered when cataract occurs in young patients.

Electric Cataract.—The great variability in the time of occurrence and the cataractogenic dose required to produce electric cataract were demonstrated by two independent reports. Belz and Vergez [54] reported the late occurrence of electric cataract 18 months after a 20-year-old youth had received a charge of 10,000 volts of electricity. Lock [32] described the remarkable case of a 22-year-old seaman who developed an electric cataract only six weeks after a burn with only a 230 to 240 volt current of less than 5 amp.

Miscellaneous.—Ostler [55] presented a case of cataract associated with pulseless disease and reviewed the literature on this condition. The late development of cataract—usually nuclear in type—often occurs. The salient features of the disease are (1) absence of palpable arterial pulsations in the upper extremities, carotids, and superficial temporal arteries; (2) arteriovenous anastomoses characteristically surrounding the optic nerve, and (3) hypersensitive carotid sinus reflex.

Alfano and Sidrys [56] saw vessels coursing over the surface of the lens in two patients with diabetes and neovascularization of the iris. They supposed these vessels were carrying aqueous, although they pointed out that this contention could not be proved in the absence of an analysis of the vessel contents.

Hagedoorn [57] reported a case with a transient cyst in the anterior capsule of the lens or between the lens capsule and the zonule which spontaneously disappeared and was not present four years after its original observation.

Sédan [58] described a dislocation of the lens into the anterior chamber following an altercation during which the patient had been hit with a wine glass. The cataractous lens remained in the anterior chamber for 35 years, and when it was removed it was found to contain a piece of glass.

Laboratory Investigations of the Lens

The Normal Lens.—Further studies on the three soluble proteins of the lens by François and Rabaey [59] showed that Fraction III was produced during embryonic life and was in highest concentration in the nucleus of the adult lens. From these findings they concluded that Fraction III was not a denaturation product of the aging Fraction I (α-crystallin) but was a distinct protein that was synthesized only during embryonic life. The increase in the insoluble albuminoid during aging was due to a large extent to the precipitation of Fraction I in the nucleus of the lens.

Green and Solomon [60] studied the effect of age upon lens metabolism by comparing the ability of extracts from lenses of one-month-old rabbits with those from 3-year-old rabbits to produce lactic acid under anaerobic conditions from glucose, glucose-6-phosphate, and fructose diphosphate. They found that the qualitative properties of the lens enzymes were not affected by age and that no shift occurred in the major metabolic pathway of the normal lens between the ages of 3 weeks and 3 years. Thus, despite an increase in over-all metabolic activity per lens, accompanying its growth and development, the metabolic efficiency per unit wet weight or per unit of protein steadily decreased with increasing age of the lens. They thought this decrease to be due to the decrease in the soluble protein which is characteristic of the aging process in the lens.

Heinrichs and Harris [61] found that the concentrations of sodium and potassium in the fresh rabbit lens did not vary with the age of the lens. However, the metabolism of the older lenses was different from that of younger lenses, since the older lenses could not recover from the "cation shift" as readily as younger lenses, unless excess quantities of glucose were supplied. Furthermore, in the absence of glucose, young lenses could recover to a certain extent unless they were incubated under anaerobic conditions. The movements of sodium and potassium under the temperature-induced "cation shift" were found to be somewhat independent, suggesting a separate physiologic "pump" for the separate ions.

Dohlman [62] studied the uptake of radioactive sulfate by the rabbit eye. He found that it was incorporated into the lens as nonsulfate sulfur. It was present to only a slight extent, but, once present, it was retained for a long time, since there was a very slow turnover rate.

The possible role of glutathione in the carbohydrate metabolism of the lens was discussed by Kinoshita and Masurat.[63] It appears that oxidized glutathione may accept the hydrogen from the reduced triphosphopyridine nucleotide, formed in the oxidative-shunt mechanism of carbohydrate metabolism. The reduced glutathione produced can be oxidized by the enzymes in the lens to oxidized glutathione. The authors feel that this may be an important step in carbohydrate metabolism, since cytochrome activity has been clearly demonstrated only in the lens epithelium. The glutathione in the lens appears to be bound to the lens proteins by hydrogen linkages, and the peptidase activity of the lens is low for hydrolyzing glutathione.

Metabolism of the Cataractous Lens.— The glutathione-containing enzyme, triosephosphate dehydrogenase, is inhibited by iodoacetic acid as well as by ionizing radiation. This inhibition produces a decrease in anaerobic glycolysis. With this in mind, Cibis, Constant, Pribyl, and Becker [64] compared the ocular effects in albino rabbits of iodoacetic acid with those produced by ionizing radiation. After intravenous injection of 20 to 60 mg. of iodoacetic acid per kilogram of body weight, exudation occurred into the anterior chamber, posterior chamber, and vitreous. In addition, the formation of aqueous was partially suppressed, the mitotic activity of the lens epithelium was inhibited, and lenticular changes developed in one to three months in 65% of the animals. Except for some slight differences, the observations made following injection of iodoacetic acid correlated exceedingly well with those seen following ionizing radiation.

A series of remarkable papers by Ogino and his co-workers [65-67] appeared. They found substances in the urine of patients with senile cataracts which were cataractogenic in ascorbic acid (vitamin C) deficient guinea pigs. In contrast, the urine from patients without senile cataract did not contain these cataractogenic substances, which the authors have identified as anthranilic acid and 5-hydroxyanthranilic acid. These acids are formed in the metabolism of tryptophan. Furthermore, one of them, 5-hydroxyanthranilic acid, forms a reversible redox system with quinoniminecarboxylic acid, a substance cataractogenic for scorbutic guinea pigs. These results suggest that the cataractogenic substance in senile cataract is quinoniminecarboxylic acid, a quinoid intermediate in tryptophan metabolism. The finding of a quinoid as the cataractogenic substance in senile cataract is paralleled by the previous discovery of other quinoid substances as the cataractogenic agents in experimental cataracts, such as β-naphthoquinone in naphthalene cataract; benzoquinone acetic acid in diabetic cataract and in the cataract formed upon administering galactose and the combination of tyrosine and sodium butyrate, and 2-amino-p-quinonimine in dinitrophenol cataract. The histologic picture of the progressive changes produced by these quinoid substances was similar to the histologic pictures of other experimental cataracts. In the early stages irregularity and sparsity of nuclei in the anterior subcapsular epithelium and vacuoles in the lens fibers at the equator were observed. As the lesions progressed amorphous material was noted in the disrupted cortical architecture and pseudoepithelial cells were found in the posterior subcapsular cortex.

Vozza [68] stated that the cataract developing in rats on a human-milk diet belongs to the group of galactose cataracts, the galactose being derived from the hydrolysis of the lactose in human milk. The development of these cataracts can be retarded by supplementing the diet of the rats with protein in the form of casein. De Vincentiis [69] found no variation in the sodium, potassium, or amino nitrogen of lens when he experimen-

tally altered the protein content of the aqueous by paracentesis or by endovitreal injections of homologous plasma or lysozyme unless dense cataracts formed. If the experimental alterations produced cataract, the sodium in the lens increased and the potassium and amino nitrogen decreased.

Snydacker [70] studied the depth of the anterior chamber and the volume of the cataractous lens in 103 eyes. He found that, in general, the larger the lens the shallower the anterior chamber. However, there were some exceptions, leading him to the conclusion that factors other than lens volume are important in determining the depth of the anterior chamber. Except for intumescence, the increase in the volume of the lens was not found to be related to the degree of maturity of the cataract.

Radiation Cataract.—The role of glutathione in the metabolism of the lens was also investigated in the study of radiation cataract. Swanson, Rose, and Taube [71] found that previous treatment with glutathione decreased the incidence of conspicuous sutures in the lenses of animals exposed to x-radiation. Furthermore, the glutathione administration produced a protection of glucose-6-phosphate dehydrogenase. In addition, if the animals were treated with glutathione there was no decrease in cytochrome oxidase activity in the lens following x-irradiation.

Van Heyningen and Pirie [72] found that the glutathione content of irradiated lenses was drastically reduced shortly after the eyes had been exposed to radiation. However, in contrast to the findings of Nordmann and Mandel,[73] they found no loss of hexokinase activity in the irradiated lenses of rabbits until they were almost completely opaque.

The species differences in the radiosensitivity of the lens were studied by von Sallmann, Caravaggio, Munoz, and Drungis. They analyzed the differences in the response of the lens in mice, rats, guinea pigs, rabbits, cats, dogs, and monkeys to doses of 1000 r of x-ray. The exposure produced depression or complete inhibition of mitosis which was short-lasting in mice and rats. This inhibition was followed in all species by an overcompensating increase in cell division, which reached the highest peaks in dogs and cats. Radiation-induced cell degeneration with nuclear fragmentation was also studied. It was found to be extensive in mice, rats, and rabbits but was surpassed by the extrusion of chromatin in dogs and cats. The distribution of the chromatin material seen in dogs and cats suggested the picture of a restoration of the relationship between nucleus and cytoplasm rather than a lethal injury to the lens. In spite of these quantitative differences, in general, the lenses of all the animals studied responded qualitatively in the same manner to the radiation, although there were variations in the extent of injury.

Von Sallmann [75] contrasted the histology of radiation cataracts with that of cataracts caused by diet. In the cataracts produced by ionizing radiations and radiomimetic drugs, damage affecting the cell nuclei in the germinative zone appeared to initiate the cataractous lesion and the cataract was progressive. In contrast, in the cataracts produced by diets containing galactose or alloxan or those deficient in tryptophan the cells in the lens epithelium of the germinative zone were but little involved; the chief effect observed was extensive damage to the lens fibers themselves. In the latter type of cataract the effect on cell division did not seem to contribute to the extensive lens fiber changes, and when the injurious factors were withdrawn new normal lens fibers were formed.

The anatomic parts of the lens most susceptible to irradiation damage were studied by Pirie and Flanders.[76] They found that no lens opacity was produced when only the axial core of the rabbit lens was irradiated with a dose that would have produced a cataract if administered to the whole lens. When the axial core alone was shielded, and the entire periphery of the lens was exposed, complete cataract appeared in three of five rabbits. However, when about one-quarter

of the periphery was shielded complete cataract did not develop. These experiments all demonstrated that the lens fibers are dependent upon the peripheral tissue of the lens and that if a small fraction of this remains healthy, the fibers will remain normal. A small proportion of the epithelial cells can exert a great effect in maintaining the health of the adjacent lens tissue. This effect in the lens is similar to that observed in the skin, where it has been shown that normal cells of skin contain some factor or factors of importance to the recovery of surrounding epithelial cells injured by x-rays.

Shapiro, Gurney, and Solari [77] determined that the usual doses of radioiodine used therapeutically would have no damaging effect on the cornea or lens. They studied the penetrance of radioactive iodine from the gastrointestinal tract to the aqueous, vitreous, and lens of rabbits. The time curves were of the same shape, with peak counts being obtained between 15 and 21 hours. The highest radioiodine counts were obtained for blood, and the lowest levels, for the lens. Aqueous and vitreous counts were intermediate. Paracentesis increased the counts in the aqueous and in the lens. Merriam [78] used phantom masks with an ionization chamber inserted in a plastic eye to reproduce the treatment conditions used for various tumors and thereby to measure the effective radiation at the lens. He found that the minimum cataractogenic dose after single exposure was 200 r; after divided doses extending over a period of three weeks to three months it was 400 r, and for divided doses extending over three months it was 550 r. In a group of patients receiving between 350 r and 550 r in divided doses over a period of three weeks to three months, about 40% developed cataract. The time of appearance of the cataract was longer in those eyes receiving the smaller doses. As the dose increased the incidence of progressive opacities also increased. All of the cases developed cataracts if they had received over 1150 r to the lens, regardless of the duration over which the treatment was spread.

Newell, Beaman, Jacobson, Marks, and Caston [79] tested the protective effect of hemopoietic cell suspension from embryo mice given subsequent to x-irradiation. It had previously been shown that such cell suspensions had improved the survival rate of lethally irradiated mice. However, the injection of the cell suspension into irradiated mice did not modify the development of radiation-induced cataract.

The Vitreous

Clinical Observations.—In an excellent article on the technique of slit-lamp microscopy of the vitreous and fundus, Goldmann [80] described the normal appearance of the vitreous and discussed the characteristics of vitreous cysts, vitreous detachments, fibrous degeneration of the vitreous, and membrane formation in the vitreous as seen with the slit-lamp microscope. Bedell [81] described fibrous proliferations in the vitreous as seen with fundus photography. Goldmann pointed out the relationship between vitreous detachment and fibrous degeneration of the vitreous and the occurrence of retinal detachment. This subject was discussed further in an informative article by Teng and Chi.[82] They distinguish two types of vitreous liquefaction. The first starts in the central core of the vitreous and has no posterior detachment of the hyaloid membrane. The second type is characterized by anterior contracture of the solid portion of the vitreous, leaving the posterior portion in a liquid form with a detachment of the posterior hyaloid membrane. Two types of vitreoretinal adhesions were also found. The first, or senile, type occurs as a broad band near the ora serrata. The second, or localized, adhesion forms at the site of a congenital rosette. It was the second type of vitreous liquefaction and the second type of vitreoretinal adhesion that were found to be invariable factors present in producing retinal detachment whenever sudden motion produced traction at the site of the adhesion.

Wadsworth [83] gave some excellent illustrations showing how vitreous bands are important in the pathogenesis of retinal detachment.

The method of treating retinal detachment by implanting vitreous in combination with a diathermy procedure was described by Shafer.[84] He reported on 72 vitreous implantations performed on 64 eyes with complicated retinal detachments that had previously been treated unsuccessfully with retinal surgery. In this series the retina was reattached in 29 eyes and no serious complications were encountered. The vitreous implanted appeared to be completely inert to the recipient eye.

Laboratory Observations.—The increase in the residual protein of the vitreous during growth of the bovine eye was studied by Boyer, Suran, Hogan, and McEwen.[85] They found a constant concentration of residual protein during the growth of the eye, demonstrating a production of residual protein during life which was parallel to the formation of the other elements of the vitreous. Green and his co-workers [86,87] found no significant difference in the distribution of bicarbonate ion in the vitreous of rabbits, whether the eye was removed from the living animal or after death. The concentration of bicarbonate was highest in the vitreous around the ciliary body. Dohlman [62] found that the normal vitreous did not show any uptake of radioactive sulfur, since the vitreous is acellular, is avascular, and does not contain sulfated mucopolysaccharides.

It does not seem that ultrasonic radiation will be of help in promoting the absorption of blood from the vitreous. Baum [88] found that ultrasonic radiation within the "safe" tissue did not influence the rate of absorption of vitreous hemorrhages in the rabbit.

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News and Comment

ANNOUNCEMENTS

Basic Course in Orthoptics for Technicians.—The Basic Course in Orthoptics for Technicians, sponsored by the American Orthoptic Council, will be held in the Department of Ophthalmology, University Hospital, Ann Arbor, Mich., from June 23 through Aug. 16, 1958. As usual, there will be didactic lectures and practical demonstrations, given by an outstanding faculty. Further information as well as application blanks may be obtained by writing John W. Henderson, M.D., University Hospital, Ann Arbor, Mich.

University of Michigan Postgraduate Conferences.—The University of Michigan Medical School announces postgraduate conferences for ophthalmologists and otolaryngologists to be held on the following dates: Otolaryngology Conference, April 17, 18, and 19; Ophthalmology Conference, April 21, 22, and 23, 1958. For further information write to John M. Sheldon, Director, Department of Postgraduate Medicine, University of Michigan Medical School, Room 1610, University Hospital, Ann Arbor, Mich.

Glaucoma Course at Massachusetts Eye and Ear Infirmary.—A one-week course in glaucoma will be given at the Massachusetts Eye and Ear Infirmary, under the direction of Dr. Paul A. Chandler, April 28 through May 3, 1958. Topics to be considered will be ocular hydrodynamics; gonioscopy, tonography, and perimetry; diagnosis, and medical and surgical management. Surgical demonstrations will be held in the operating room. Patients will be available for demonstration and examination. Admission will be limited to ten persons. Fee: $100.

Application may be made to Dr. E. B. Dunphy, Chief of Ophthalmology, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston 14.

New York Eye and Ear Infirmary Spring Meeting.—The Alumni and Staff of The New York Eye and Ear Infirmary, 218 Second Ave., New York, will hold their annual spring meeting from April 21 to 24, 1958. Seminars will be held in the mornings in ocular pathology, retinal detachment surgery, glaucoma, ocular injuries, cataract surgery, and motility. Clinical courses will be given in the afternoons as well as closed-circuit television programs.

Irish Ophthalmological Society.—The Irish Ophthalmological Society will hold its annual meeting in Dublin on May 1, 2, and 3, 1958. The Montgomery Lecture will be given by Professor Hagedoorn, Amsterdam, in Trinity College, Dublin, on Thursday, May 1.

Courses in Slit-Lamp Biomicroscopy and Ocular Surgery.—The Committee on Postgraduate Education of the Montefiore Hospital announces an advanced course in slit-lamp biomicroscopy of the living eye combined with additional courses in slit-lamp microscopy, gonioscopy, deep vitreous and retinal biomicroscopy, indirect ophthalmoscopy, surgery of intraocular foreign bodies, and retinal detachment surgery, to be given by the Montefiore Department of Ophthalmology under the direction of Dr. Harvey E. Thorpe and associates. These courses will be given at the Montefiore Hospital, Pittsburgh, May 5 to 8, 1958, inclusive, from 8 a. m. to 4 p. m. Guest speakers: Dr. Robert J. Masters, Indianapolis, and Mr. Lee Allen, Iowa City. For further information write to A. McNabb, Secretary of Postgraduate Ophthalmic Courses, 206 Iroquois Building, Pittsburgh 13.

ANNUAL MEETING OF AMERICAN MEDICAL ASSOCIATION

San Francisco, June 23-27, 1958

SECTION ON OPHTHALMOLOGY

Tuesday, June 24, 1958

Chairman's Address:

DOHRMANN K. PISCHEL, San Francisco

Address of Invited Foreign Guest: Indications for Clinical Electroretinography

PROF. GOSTA KARPE, Stockholm, Sweden

Conjunctival Flaps in the Treatment of Corneal Disease with Special Reference to New Techniques of Application

TRYGVE GUNDERSEN, Boston

Discussion to be opened by PHILLIPS THYGESON, San Jose, Calif.

The Treatment of Retinoblastoma by X-Ray and Triethylenemelamine

ALGERNON B. REESE, New York

GEORGE A. HYMAN, New York

NORAH DUV. TAPLEY, New York

ARNOLD W. FORREST, New York

Discussion to be opened by MICHAEL J. HOGAN, San Francisco

Galactosemia with Associated Cataracts in Children

WARREN A. WILSON, Los Angeles

Discussion to be opened by HAROLD F. FALLS, Ann Arbor

The Neurosurgeon's Role in Acute Visual Failure

ALFRED UIHLEIN, Rochester, Minn.

C. WILBUR RUCKER, Rochester, Minn.

Discussion to be opened by WILLIAM E. KREWSON, III, Philadelphia

Ocular Signs and Prognosis in Subdural and Subarachnoid Bleeding in Young Children

ROBERT W. HOLLENHORST, Rochester, Minn.

HAROLD A. STEIN, Rochester, Minn.

Discussion to be opened by DONALD J. LYLE, Cincinnati

"Dutch-Treat" Cocktail Party in Honor of the Chairman

5:30 to 7 p. m., $3.00 per person; Terrace Room, Fairmont Hotel

all physicians attending Section meeting and their wives are invited

Wednesday, June 25, 1958

Executive Session

The Prognosis of Melanomas of the Iris Following Excision by Iridectomy: A Study of 108 Cases in the Registry of Ophthalmic Pathology

BENJAMIN RONES, Washington, D. C.

LORENZ ZIMMERMAN, Washington, D. C.

Discussion to be opened by GEORGIANA DVORAK THEOBALD, Oak Park, Ill.

Diseases of the Macula: Basic Histopathologic Processes in Retina, Pigment Epithelium, and Choroid, Which Modify Their Clinical Appearance

BERTHA A. KLEIN, Chicago

Discussion to be opened by WILLIAM C. FRAYER, Philadelphia

Clinical and Laboratory Experiences with Virac, a Bactericidal, Fungicidal, and Viricidal Agent

JOHN E. HARRIS, Portland
PETER P. ROWELL, Portland
OLIVE BEAUDREAU, Portland
Discussion to be opened by HENRY F. ALLEN, Boston

The Effect of Tonography and Other Pressures on the Intraocular Blood Volume

JEROME W. BETTMAN, San Francisco
VICTOR FELLOWS, San Francisco
PETER CHAO, San Francisco
Discussion to be opened by BERNARD BECKER, St. Louis

Thursday, June 26, 1958

Panel on Retinal Detachment

A Scleral Imbrication Technique

ALBERT N. LEMOINE JR., Kansas City, Kan.
JAMES T. ROBISON JR., Kansas City, Kan.
LARRY T. CALKINS, Kansas City, Kan.

An Evaluation of Ophthalmoscopy After Retinal Detachment Surgery

ARIAH SCHWARTZ, San Mateo, Calif.

Retinal Detachment Surgery

JAMES S. SHIPMAN, Camden, N. J.

The Old Versus the New

JOHN W. HPNDERSON, Rochester, Minn.

The Importance and Employment of Diathermy in Today's Retinal Detachment Surgery

GRAHAM CLARK, New York

Further Experience with Vitreous Implants in Old Retinal Detachments

DONALD M. SHAFER, New York

Diathermy or Scleral Resection

JOSEPH A. C. WADSWORTH, New York

The Application of Ultrasonic Locating Techniques to Ophthalmology: II. The Ultrasonic Slit Lamp

GILBERT BAUM, Bronx, N. Y.

Discussion to be opened by
S. RODMAN IRVINE, Beverly Hills, Calif.
PETER C. KRONFELD, Chicago
P. ROBB MCDONALD, Philadelphia
A. D. RUEDEMANN SR., Detroit

Books

L'occhio nel diabete mellito. By G. Alagna and F. Scullic, with a preface by G. Martino. Price, not given. Pp. 190, with 89 illustrations. Casa Editrice G. D'Anna, Messina-Firenze, Italy, 1957.

For those who read Italian this is a well-written account of the pathology of the eye caused by diabetes. The material is divided into chapters on an anatomical basis, detailing the effects of diabetes on the various eye structures, and separate chapters in which disturbances of function are described, e. g., the ocular adnexa; the cornea, iris, and retina, and light sense, changes in refraction, and ocular tension. The illustrations are good, although not many are original.

Heredo-Retinopathia Congenitalis. By Carl Henry Alstrom, in collaboration with Olof Olson. Price, not given. Pp. 178, including bibliography and pedigree charts. Berlingska Boktryckeriet, Sweden, 1957.

This study reports on a series of 175 cases of a hitherto-unreported hereditary form of congenital blindness diagnosed as congenital retinochoroiditis, which shows a familial incidence and a high frequency in marriages of first cousins noted by Sjögren more than 25 years ago. The name heredoretinopathia congenitalis, monohybrida recessiva autosomalis, is suggested for this disease. Vision is defective at birth and consists of either total blindness or greatly impaired sight with loss of central vision and gradual deterioration of any remaining vision. The fundi show peripheral retinal pigment which is generally diagnosed as retinochoroiditis, degeneration of the retina, or tapetoretinal degeneration. Atrophy of the retina proceeds until large areas of the sclera are involved. Cataract and keratoconus are common associated features. The disease is not combined with any psychiatric or neurologic disorder. There is no increased frequency of deafmutism in these patients nor in their relatives, and no patient showed the classic features of pigmentary degeneration of the retina.

Contributions to the History of Ophthalmology. By M. Amsler, H. Arruga, F. Berg, S. Duke-Elder, R. Onfray, G. Ovio, A. Pillat, F. Rintelen, and W. P. C. Zeeman. Price, not given. Pp. 119. S. Karger AG., Arnold Böcklinstrasse 25, Basle, 1957.

Only one of the nine contributions to this supplement of *Ophthalmologica* is in English: "The History of Ophthalmology of Britain," by Sir Stewart Duke-Elder. For those who read German, French, and Italian, all of the articles are of interest, dealing with the development of ophthalmology in various countries of Europe. Many in this country who read German will be particularly interested in Pillat's article on the history of ophthalmology in Vienna.

Surgery in World War II: Ophthalmology and Laryngology. Edited by Col. John Boyd Coates Jr. Price, $5.00. Pp., 605, with numerous illustrations and tables. U. S. Government Printing Office, Washington 25, D. C., 1957.

The Office of the Surgeon General, Department of the Army, is publishing a series of volumes on the official history of the Medical Department of the United States Army in World War II. The record of achievement which is unfolded in the present volume on ophthalmology and otolaryngology is one of which all members of these two specialties can be proud. The first 378 pages, devoted to ophthalmology, have been very capably edited by M. Elliott Randolph, M.D., formerly Lieutenant Colonel and Chief of the Ophthalmology Branch of the Surgical Consultants' Division, Office of the Surgeon General, from its activation on April 15, 1944, until Feb. 22, 1945, and again from Dec. 8, 1945, until April 1, 1946. This portion of the volume discusses both the administrative and the scientific problems pertaining to ophthalmology during the last war. The opening chapter reviews the administrative evolution of ophthalmology from 1916

until the end of World War II. During World War I, and until World War II was well advanced, ophthalmology had been included in the section of head surgery under the division of surgery. On April 15, 1944, the Ophthalmology Branch of the Surgical Consultants' Division, Office of the Surgeon General, was established. Derrick Vail, M.D. (Col.), and Trygve Gundersen, M.D. (Major), followed M. Elliott Randolph in this capacity.

The short supply of ophthalmologists was a problem throughout the war. Confronted with this shortage, the Office of the Surgeon General made earnest attempts to classify and properly utilize each ophthalmologist on active duty and at the same time establish eye centers which insured proper sorting of patients. This also permitted the saving of manpower by assignment of young and more inexperienced officers to work under the supervision of mature persons with great experience. Many other administrative problems, although of less basic importance, were encountered. The problem of providing spectacles for personnel who needed them for maximum efficiency in performance of duty was one of great magnitude. The ultimate solution included, among other steps, portable overseas optical units. The history of the development of the acrylic eye now in universal use in civilian life is presented in a very interesting manner. Parallel with this, various prosthetic devices for different fields of surgery were developed, utilizing acrylic.

Administrative and scientific aspects of ophthalmology peculiar to specific theaters of war were reviewed in the Mediterranean by Trygve Gundersen, M.D. (Major), the European theater by Derrick Vail, M.D. (Col.), and the Southwest Pacific and Pacific Ocean areas by Webb Chamberlain, M.D. (Major).

James N. Greear, M.D. (Lieut. Col.), known to have been a guiding light in the rehabilitation of blinded casualties, presents an interesting history of the development of that program. Many principles were established which are being utilized in civilian life at the present time. Other sections of the book include the management of intraocular foreign bodies, uveitis, retinal detachment, cataracts in military personnel, nutritional amblyopia, night blindness in military personnel, visual disturbances associated with head injuries, plastic surgery of the lids and orbit, and chemotherapy and antibiotic therapy in the zone of the interior as it pertained to ophthalmology. These sections are all written by authors who, with their excellent prior training and extensive experience acquired during World War II, are established authorities in their fields. Since the war is now more than ten years behind us, some of the material in the book is outdated, but most of it is still of great value. The book can be read with interest by all ophthalmologists whether or not they participated in a direct way in these activities. Its value is emphasized by the present state of world unrest. Should this country become embroiled in another war, the battle ground and hence the casualties will be at the door-step of all of us and every physician will be better prepared for having perused this volume.

The Visual Pigments. By H. J. A. Dartnall. Price, $6.00. Pp. 216, with numerous graphs and illustrations. John Wiley & Sons, Inc., 440 4th Ave., New York 16, 1957.

This is a highly technical but authoritative monograph on the biology of visual pigments by one who has done a great deal of work in this field—Dartnell being the English equivalent of Wald in this country. The book is far too technical for the average ophthalmologist, since it is largely concerned with the details of the chemistry and physical properties of the various pigments found in the animal kingdom subserving the function of photoreception. For those actively engaged in this field, however, the book will be warmly welcomed.

After a short introduction to visual pigments and their photoproducts, the chapters deal with the physical chemistry of rhodopsin, the structure of rhodopsin, isomerism and visual pigments, the homogeneity of visual pigment solutions, and various methods available for the experimental approach to the problems of photochemistry. Each chapter includes an excellent bibliography.

Guide to Medical Writing. By H. Davidson, M.D. Price, $5.00. Pp. 338, with 12 illustrations. The Ronald Press Company, 15 E. 26th St., New York 10, 1957.

The fact that physicians as a class are generally mediocre writers is attested to by the large number of books on the market purporting to improve the quality of their output. These manuals describing what is wrong with their manuscripts, and telling them how they can be improved, have been coming off the press in increasing numbers and show that either doctors do not care how they write or that editors of medical journals will accept manuscripts which would be turned down flat by the staffs of nonscientific magazines. Both were probably true a few years ago, but today our medical journals have a plethora of material to publish and their editors can be more particular and turn down those which do not come up to minimum standards in presentation and style.

In this new book Dr. Davidson, who has been editor-in-chief of the *Journal of the Medical Society of New Jersey* since 1941 and is an author of several books, does what no one else has attempted up to now: He approaches his subject from a common sense and humorous point of view. His thesis is that once an article has appeared in medical literature it has become immortal. The doctor who wrote it must necessarily die, but his work lives on forever. Hence, it behooves him to leave behind only the best of which he is capable. By giving numerous examples of poor writing and how each can be improved, he drives home his points far better than those pedagogical books on medical writing, of which we have plenty, which read like textbooks of physics and bore one to distraction. Dr. Davidson has an unusual knack of selecting excellent examples to demonstrate how much better one way of phrasing something is than another. These are so interesting and frequently humorous that reading his book becomes a pleasure instead of a painful process of learning something.

In addition to improving one's ability to write, Dr. Davidson gives some excellent advice on how to handle medical arithmetic. He points out the frequency with which authors have misled themselves and published data which should never have appeared in print because they failed to run adequate controls and mathematically their results were merely due to chance. He specifically shows how these errors can be avoided by listing a number of fallacies, such as "the fallacy of the normless base," "the fallacy of the mixed population," of "the wrong way addition," of "the skinny sample," and the "post-hoc" fallacy.

The book is literally crammed with practical advice of value to everyone who attempts to write a medical paper. If ophthalmologists would buy this book and read it before submitting a paper for publication the value of our literature would rocket immediately, and the number of papers rejected would decline.

Introduction to Anesthesia. By R. D. Dripps, J. E. Eckenhoff, and L. D. Vandam. Price, $4.75. Pp. 266, with 47 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

Although not devoted to general anesthesia in ophthalmic operations, this is an extremely valuable book for every department to have in its library. The book is divided into five sections, four of which deal with the care of the patients. In Section I, the preanesthetic period, procedures are advocated for preanesthetic rounds, with guides to preanesthetic medication and the choice of the anesthetic for the particular patient. Section II deals with the day of anesthesia and largely concerns the actual administration of the anesthetic and theoretical considerations which are of chief interest to the anesthetist. Section III concerns the hazards during operation and determination of the depth of the anesthesia, fire and explosion hazards, and unusual complications of anesthesia. Section IV, entitled "The Postoperative Period," deals with the hazards of the immediate postoperative period, the recovery room, and treatment of immediate postoperative pain and excitement. Under special topics there is an excellent chapter on cardiac resuscitation. The book is compact and is written in readable style and has excellent line drawings by the junior author.

Medical Radiation Biology. By Friedrich Ellinger. Price, $20.00. Pp. 945. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1957.

This is a timely book which presents in textbook form the effects of radiation on man in conditions of both health and disease. For those of us who are neophytes in the physics of radiation and its effects on life processes in the cell, this book offers an easy and thoroughly understandable introduction. The first part of the book deals with the general principles of radiation and the effect of radiant energy on living matter. The specific chemical effects of radiant energy on water, proteins, amino acids, sulfhydryl compounds, enzymes, etc., is then reviewed, and the fundamental aspects of radiosensitivity are briefly outlined. The remainder of the book concerns the effects of radiation on the various organs of the body and on such physiological processes as metabolism and on progeny. The results of radiation on diseased tissues is then dealt with. The section on the effects on the eye is regrettably short, but this is understandable in a book which is already 945 pages in length. The bibliography is not the least important part of the book, the author listing 4600 references. It should be an important book in the library of any ophthalmological department or library.

Management of Complications in Eye Surgery: Avoidance of Pitfalls and Treatment of Difficult Situations in Ophthalmologic Operations. Edited by R. M. Fasanella, M.D. Price, $16.00. Pp. 422. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

Although this volume with its twenty-two contributors lacks continuity, it is full of practical suggestions on the prevention and treatment of most of the complications encountered in ocular surgery. To offset the inevitable variance of style found in texts with multiple authors, the editor has arranged the material in an orderly and more or less uniform manner. Each chapter is an entity in itself, in which the author discusses the management of the particular problem at hand. There is marked variation in the completeness with which the subjects are covered.

Among the outstanding contributions are the discussions on ptosis, cataract, delayed re-formation of the anterior chamber, and retinal detachment. Some of the others are sketchy, with inadequate bibliographies, and add little to the value of the text. However, in spite of these shortcomings the book is heartily recommended; for its virtues greatly outweigh its faults. The ophthalmic surgeon will find in it many valuable hints that will aid him in his everyday surgery. The printing is very good; the reproductions are clear, and the whole format is excellent.

Practical Refraction. By Bernard C. Gettes, M.D. Price, not given. Pp. 170. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1957.

The material for this book on the practical aspects of refraction was derived from the teaching of residents and postgraduate students in Philadelphia. It does not consider—and therefore is intended to supplement books on—anatomy, physiology, geometric and physiologic optics, heterophoria, and motility disorders. In exceedingly clear style, different refraction techniques are applied to the problems of patients, with sufficient nontechnical background material for understanding of the principles used, e. g., subjective methods in the determination of astigmatism and accommodation and special problems in handling the hypermetropic, myopic, and presbyopic patient. An evaluation of the use of the latest cycloplegic drugs is given. There is a short chapter on the indications for the use of contact lenses and an excellent discussion of the various types of ophthalmic lenses with their advantages and disadvantages in specific types of cases. This should help the ophthalmologist greatly in prescribing the correct form of lens or in checking the optician. Strong reading adds have been found more satisfactory than telescopic lenses for patients with subnormal vision, and the author believes that the ophthalmologist should be more aware of his responsibility to give these partially-sighted persons their best potential vision and thus keep them out of the hands of the unscrupulous.

Although the author states that his book is designed for beginners, it does not give detailed steps in the technique of refraction, especially streak retinoscopy with cylinders. It assumes that the student has already had basic work in optics and some clinical experience in technique and is ready for sound advice on the management of the refraction patient. Unless the mature practicing ophthalmologist has made a special effort to keep up with the recent trends and methods of refraction, he would find much of practical value in this small volume.

Slit Lamp Gonioscopy. By G. Gorin and A. Posner. Price, $7.00. Pp. 176, with 67 illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

Gonioscopy, like slit-lamp microscopy, has become a necessary routine office procedure, and no ophthalmologist can afford to treat patients with glaucoma unless he acquires this technique. This manual is presented for the purpose of acquainting the ophthalmologist untrained in gonioscopy with the principles and techniques he must learn and acquire in order to interpret pathological changes in the chamber angle. The history of the development of gonioscopy is sketched, and the anatomy of the angle in man and the comparative anatomy in animals are described.

The technique of gonioscopy is described, with use of a slit-lamp for illumination, which necessitates the patient being examined in the sitting position and imposes the added difficulty of focusing a slit beam. While there are undoubtedly certain advantages to slit-lamp gonioscopy as compared with gonioscopy with a Barkan lamp, it seems to this reviewer that this imposes an unnecessary difficulty for the novice and that the authors should have presented the beginners with the easier technique at first, and written a separate chapter on the special technic of slit-lamp gonioscopy. Since they use a slit lamp, they recommend the Goldman lens and the Allen (or Allen-Thorpe) gonioprism. Any modern slit lamp may be used. They recommend the Haag-Streit, Bausch & Lomb, and Clement Clarke Lamps.

The chamber angle in normal eyes is described, followed by the appearance in chronic simple open-angle glaucoma; in angle-closure glaucoma; in special forms such as glaucoma capsulare, glaucoma secondary to central vein thrombosis, and aphakic glaucoma, and, finally, the findings in secondary glaucoma and congenital glaucoma. The angle after operations to relieve glaucoma, the appearance of tumors, and the result of injuries are covered. There is a good bibliography. The illustrations are good, and the style and printing are excellent.

Traitement chirurgical des affections oculaires, Vol. I. By L. Guillaumat, R. de Saint-Martin, L., Paufique, S. Schiff-Wertheimer, and G. P. Sourdille. Price, 6500 fr. Pp. 439, with 105 illustrations. Gaston Doin & Cie, 8 place de l'Odéon, Paris, 1957.

This is the first of three volumes covering the surgical treatment of diseases of the eyes. This volume includes a section on general surgical principles, the surgery of cataract, glaucoma, iridocyclitis, and injuries. The illustrations are good and sufficient to make the book of value even for those who do not read French fluently.

System of Ophthalmic Illustration. By Peter Hansell. Price, $5.75. Pp. 114, with 78 illustrations. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1956.

This book will be of value to every department of ophthalmology in which the techniques of visual representation are important from the point of view of teaching and presentation of research. It is certainly true that many excellent manuscripts are spoiled by being served up with poor illustrations. Granted that an author has something to say, the Chinese proverb still holds. This book endeavors to show one how to make a good illustration. Obviously, the book is well illustrated, but the important part is that the author tells the reader just what makes the illustration good. There are chapters on photography and much sound advice on the choice of camera, lighting equipment, and methods which should be employed in studio, ward, operating room, and consulting room. Motion-picture photography,

stereoscopic photography, keratography, slit-lamp photography, infrared and ultraviolet photography, and photography with the gonioscope are all dealt with. The ophthalmic artist is the title of a chapter summarizing the functions of the artist and pointing out present deficiencies in photography when this is employed exclusively, for example, retinal photography. If any criticism is to be made of the book, it is that it is too short. The author has had a tremendous experience in the field and has leaned backward in making a modest contribution. In future editions, this book, which is sure to be popular, will gain by expansion.

Symposium on Diseases and Surgery of the Lens. Edited by George M. Haik. Price, $10.50. Pp. 270, with 233 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1957.

This volume of Proceedings of the Fifth Annual Session of the New Orleans Academy of Ophthalmology concerns the lens, with the largest emphasis on the extraction of cataract. A group of distinguished ophthalmologists and scientists comprised the panel. The twelve sections of the book are titled as follows:

(1) Embryology of the Lens
Frederick C. Cordes

(2) Types of Congenital and Juvenile Cataracts
Frederick C. Cordes

(3) Diagnosis and Classification of Adult Cataracts
Harvey E. Thorpe

(4) Surgery of Congenital Cataracts
Frederick C. Cordes

(5) The Techniques and Mechanics of the Cataract Operation
Derrick Vail

(6) Surgery of Complicated Cataracts
Paul A. Chandler

(7) Complications During Cataract Extraction
Paul A. Chandler

(8) Normal Healing of the Cataract Incision
John H. Dunnington

(9) Complications in Congenital Cataract Surgery
Paul A. Chandler

(10) Complications of Wound Healing After Cataract Surgery
John H. Dunnington

(11) Vitreous Changes Before and After Cataract Extraction
S. Rodman Irvine

(12) Lens-Induced Uveitis and Glaucoma
S. Rodman Irvine

Following this, 36 pages are devoted to round-table discussions, which to many form the most valuable part of the symposium. Dr. V. Everett Kinsey participated in the round-table discussions, and the moderators were Drs. James H. Allen, William B. Clark, and George M. Haik. All of the published symposia of the New Orleans Academy have been valuable contributions to our literature, and this one is no exception.

Augensymptomen bei Hirntumoren. By A. Huber. Price, $14.00. Pp. 404, with 192 illustrations. Hans Huber, Marktgasse 9, Bern, 16, 1957.

The frequency of ocular signs and symptoms as the initial occurrence in the patient with a brain tumor is brought out by the author's figures that 60% of his cases presented eye signs as an initial complaint. This book, in German, details the methods of a neuro-ophthalmological examination which should be carried out in a patient suspected of a brain tumor. The general symptoms and signs due to increased intracranial pressure are described, followed by the local symptoms. Chapter IV relates the relationship between the eye signs and the nature of the tumor, and Chapter V covers pseudotumors. The last chapter summarizes the author's experiences with 1600 cases seen in the neurosurgical clinic of the University of Zurich.

For those who read German fluently this is a very valuable book; for the author has had a wide experience with brain tumors and has carefully reviewed and documented all his cases. The illustrations are excellent.

Brain and Consciousness. By Hartwig Kuhlenbeck. Price, sFr. 34.60. Pp. 344. S. Karger AG., Arnold Böcklinstrasse 25, Basel, 1957.

This is a highly philosophical essay on the relationship of brain and consciousness. The author divides his material into the following sections: (1) the materialistic approach, dealing with the physical world and, in particular, the nervous system; (2) the idealistic approach, which is entirely philosophical, and, finally, (3) the postulational psychophysical parallelism, the latter being somewhat similar to the approach of Wiener in cybernetics.

Light, Color and Vision. By Yves LeGrand, translated by R. W. Hunt, J. W. Walsh, and E. R. Hunt. Price, $11.00. Pp. 512, with 125 illustrations. John Wiley & Sons, Inc., 440 Fourth Ave., New York 16, 1957.

Only those ophthalmologists who have a background of physics and mathematics will be able to read this book with pleasure. This is regrettable, since the book is an extremely valuable exposition of retinal physiology. One is forced to admit that the author is not to blame but that the educational system of teaching premedical students mathematics and physics is defective. The fact that most of us have trouble with mathematics is not due to the difficulty of the subject but to the way in which it is presented, and this is being increasingly realized by educators. It is too late for those of us who are past the residency stage to rectify the inadequacies of our education, but for those coming into ophthalmology an exposure to more mathematics is highly advisable.

The book is divided into two sections. The first deals with experimental facts. This carries the reader through the physics of radiation, a short description of visual receptors, the methods employed in photometric quantitation, the basic principles of colorimetry, absolute thresholds, luminance difference thresholds, color difference thresholds, time effects, spatial interactions, and anomalies of color vision. The second section describes the theories of vision and deals with what one might call the known physiology of the eye. In the appendix there are exercises covering the material, with their solutions, to serve as a means of determining the student's understanding of the book. This reviewer sadly admits that he could not solve even 1 of the 45 problems posed. For the rare person who has had the proper bringing up, this book will be extremely valuable and interesting.

Blindness in Children. By M. Norris, Spaudling, and Brodie. Price, $3.00. Pp. 173, with 8 pages of illustrations. The University of Chicago Press, 5750 S. Ellis Ave., Chicago 37, 1957.

This book is the outcome of a study of 66 blind preschool children selected from a total of 295 cases known to The University of Chicago Clinics and to the Illinois Department of Public Welfare. Eighty-five per cent of the selected group were blind as a result of retrolental fibroplasia. The remaining group were full-term children with a variety of other eye conditions.

The selected group were studied intensively by trained psychologists and measured against normally sighted groups of similar age and socioeconomic levels. A matched control group was found to be impossible to obtain. It was found that blindness itself did not change the normal mental functioning of these children or their over-all development. When function did seem to be retarded in the blind children, it did not necessarily mean that it was evidence of a basic mental defect. No evidence was secured that retrolental fibroplasia is associated with either a specific or a generalized brain defect. One of the most interesting and probably equally important findings was the following, quoted to assure accuracy: "The earliest months of the blind child's life and the years of the preschool period are of primary importance. They determine the course of his later development. All the components for the healthy personality development of any child are critical for the blind child because his capacity to master his environment is definitely

related to his security in his family and the understanding that family members have of his needs. The damage that is done by prolonged failure to provide satisfaction of these needs is apt to be permanent. It can only be partially alleviated by later treatment."

The book is well documented, with six illustrative case histories, the details of which will be obviously of more interest to child psychologists than to ophthalmologists. The value of the book for the eye physician is chiefly in trying to form some basis for mutual understanding between the social worker and psychologist and himself, so that the mutual problem of the blind child can be worked out to the best of the child's advantage. Certainly the ophthalmologist should not attempt to solve all the problems which these blind children pose for both the community, their parents, and themselves. The paragraph quoted above is evidence that expert help is needed, and needed early. If this book does no more for the ophthalmologist than to awaken him to this realization, it will have served a very useful purpose. Its value as a psychological document will have to be judged by those trained in this field.

Atlas of Eye Surgery. By R. T. Paton, H. M. Katzin, and D. Stillwell. Price, $15.00. Pp. 248, with 463 illustrations. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1957.

This atlas was planned by the authors as a text for residents in ophthalmology with the thought in mind that by meticulously outlining each step in a surgical procedure its difficulties could be minimized, so that when the time came for its performance on the patient a large part of the learning process would have been accomplished. This is a sound pedagogic principle, for visualization of acts is always helpful in learning manual skills. The follow-through in tennis or golf, the correct drop of the wrist in bowing, and all other simple but seemingly complicated and vitally important movements can best be acquired by having a mental picture firmly in mind before the actual experience. To this end, a correct combination of a few well-chosen words and many illustrations are needed. The authors have admirably accomplished their purpose, for 90% of this text is illustrations, and the remainder, concise explanations of what each illustration intends to demonstrate.

Eight basic groups of operations are described, each representing a specific type of procedure whose technical skill it is necessary for every eye surgeon to master. The cataract operation naturally takes the greatest portion, occupying 80 pages. Operations for glaucoma, retinal detachment, corneal transplantation, removal of an eye, strabismus, and pterygium follow, each described in clear-cut line drawings, which even without shading are so beautifully executed that they stand out in three dimensions in almost all instances. Occasionally Miss Stillwell has found it necessary to supplement the basic drawing with a cross sectional diagram in order to show the position of a knife needle in a three-dimensional space. A unique addition to the section on retinal detachment is a muscle chart for the right and left eyes showing the standard measurements of landmarks which are useful to the surgeon in performing operative procedures.

Corneal transplantation has naturally been given considerable emphasis, owing to the authors' preeminence in this field, and, while one might comment that in a text designed for residents undue space has been allotted for these procedures, for those more advanced and called on to do transplants routinely this section will prove to be most valuable.

No claim is made for originality in any of the procedures presented, and the authors state that they have accepted suggestions from all sources and have revised their methods when new instruments appeared or old ones were improved. Their chief emphasis has been to suggest methods which time has shown them are essentially the safest for those of average skill to employ.

Headache: Diagnosis and Treatment. By Robert E. Ryan. Second edition. Price, $6.75. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1957.

Headache is one of the commonest symptoms for which patients consult the general practitioner, ophthalmologist, and otolaryngologist. This book discusses the different pathologic conditions which produce headache and which are likely to be met by all physicians. Some of the chapters in the book will be of definite value to ophthalmologists. Chapter 12 deals entirely with ophthalmic migraine; Chapter 26, with temporal arteritis, and Chapter 31, which was written by Dr. Leslie Drews, is entirely limited to headache or head pain due to ophthalmological causes and is a thorough and practical review of this subject. In this second edition several new syndromes are discussed and new diagnostic procedures and approaches to therapy have been added.

Corneal Grafts. Edited by B. W. Rycroft. Price, $13.50. Pp. 285, with 155 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

This book is composed of a series of manuscripts by various well-known authors on the subject of keratoplasty. The editor, Dr. Rycroft, has written the chapters on the history of keratoplasty, special instruments to be used in the performance of the operation, and the results of his own cases and those reported in the literature. He has also assembled an excellent bibliography arranged in alphabetical order. The other chapters are as follows:

Anatomy and Physiology of the Cornea	Hugh Davson
The Histopathology of the Corneal Graft	Guy Offret
Indications for Corneal Transplant and Selection of Cases	A. Franceschetti and G. Maeder
Full-Thickness Grafts	J. A. Barraquez-Moner
Lamellar Keratoplasty	Louis Paufique
Keratectomies-Retransplants	Ramon Castroviejo
Special Methods	G. P. Sourdille
General Complications of Corneal Grafting	J. W. Tudor Thomas
Contact Lenses and Corneal Grafts	Frederick Ridley
Special Features of Keratoplasty	Marc Amsler
The Preservation of the Donor Graft	R. E. Billingham and B. W. Rycroft
The Biological Problem	A. E. Maumenee
Donor Material and the Law	R. Townley Paton

The book contains a wealth of material arranged in a scholarly and compact form, with a good index, which makes the book useful from a practical point of view. It is a very real contribution to the literature on corneal grafting.

The Doctor Eyes the Poor Reader. By Delwyn Schubert, Ph.D. Price, $3.75. Pp. 101. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1957.

This book was written by the director of the Reading Clinic, Los Angeles State College of Applied Arts and Sciences, to assist ophthalmologists to discuss intelligently with parents the problems of the poor reader. He points out that most ophthalmologists do not have the time or background to digest the mass of literature on this subject. He emphasizes the fact that reading failure is the result of a complex combination of factors rather than any simple cause and that in order to approach the problem scientifically a team of specialists must pool their findings, each from a different point of view. For example, physical factors are often involved, such as poor health, visual anomalies, auditory handicaps, endocrine dysfunction, and physical immaturity; also, mental, emotional, and social immaturity may play a dominant role in reading retardation, and, finally, such factors as confused dominance must be investigated. All of these factors have to be evaluated in the individual case. He emphasizes the point that no one factor can be singled out to explain reading failure in all cases. His remarks on confused dominance as

a cause of dyslexia are particularly interesting. He states that several dominance theories have been set forth to explain readily disability but none has been proved, and there is as yet no consensus as to the relationship between dominance problems and reading disability.

The child's reading difficulties should be matched against his general intelligence. The results of intelligence tests are expressed in two type of scores: mental age, or MA and intelligence quotient, or IQ. The two tests which he believes give bona fide indications of a poor reader's mental potential are the Stanford-Binet and the Wechsler Intelligence Scale for children. There are an excellent chapter on the role of the medical consultant and a chapter entitled, "How and by Whom Poor Readers are Given Help." The least valuable part of the book is probably the chapter entitled, "Doctor, How Are Your Reading Skills?" In this the author states that he has guided many professional persons in reading improvement courses and that "one twelve week course offered for adults through the Los Angeles Evening Division resulted in an average rate increase of 172 words per minute with no loss of comprehension."

It is always questionable how much of the improvement in reading skills comes about by the person's immediate concentration on the fast reading rather than by any skill acquired by virtue of the procedures followed. The situation is somewhat comparable to the courses offered to help one improve his memory. By concentrating on fixing things in one's memory it is, of course, possible to demonstrate an immediate improvement, but whether this lasts after the course is over is questionable.

The Sheard Volume: Visual and Opthalmic Optics. By Charles Sheard. Price, $15.00. Pp. 467, with numerous line drawings. Chilton Company, Book Division, 5605 Chestnut St., Philadelphia 39, 1957.

Dr. Charles Sheard has had considerable influence on the development of optics and visual physiology in this country. In 1952 at a meeting of the American Academy of Optometry in Rochester, N. Y., a number of papers were presented on applied physiological optics, one of which was contributed by Dr. Sheard. Many of those present felt that all of Dr. Sheard's contributions should be combined in one volume, since it was apparent that his work was not confined to optometry and optometric publications but spread into the field of opthalmology and opticianry. A sponsoring committee was established which represented all these three disciplines.

The contents of this volume include selections from editorials and short essays, largely published in the *American Journal of Physiological Optics,* of which Dr. Sheard was the Editor-in-Chief, followed by practically all of his papers published in this country and abroad. A biographical sketch and a bibliography of his published writings are appended. He published 298 papers covering a tremendously wide field of subjects. From 1924 to 1949 he was Director of the Division of Physics and Biophysical Research of the Mayo Clinic, where he is now Director Emeritus and Professor Emeritus. The committee has done ophthalmology a real service in bringing together the writings of this great scholar and researcher where they may easily be consulted.

Physiology of the Nervous System. By E. G. Walsh. Price, $9.50. Pp. 563. Longmans, Green & Co., Inc., 55 Fifth Ave., New York 3, 1957.

The primary purpose of this book is to afford clinical neurologists a clear account of the physiology of the nervous system and to afford the advanced student in physiology a summary of neurophysiology and an adequate working bibliography. The clinical ophthalmologist will perforce find much of interest in the basic physiology of the nervous system which underlies clinical neuro-ophthalmology. In addition to this, the chapter on the visual system affords an excellent review of the physiology of the eye.

The Problems of Vision in Flight at High Altitude. By Thomas C. D. Whiteside. AGARD Series, AGARDograph 13. Price, $5.00. Pp. 162, with 64 illustrations. Interscience Publishers, Inc., 250 Fifth Ave., New York 1, 1957.

The publication of this book was sponsored by the Aero-Medical Panel of the Advisory Group for Aeronautical Research and Development, North Atlantic Treaty Organization. The various problems which are met in flight at high altitudes have been attacked by the author, and the book is presented from the point of view of the investigations he has made in establishing the factors involved in these problems. After a brief introduction outlining the differences in flight under present conditions from those of the early days of aviation and, in particular, the new features due to high altitudes, the various problems encountered are grouped in the following categories: (1) the effects of changes in intensity and spectral distribution of sunlight at high altitudes, (2) the physiological changes affecting visibility of objects inside the cockpit, and (3) physiological factors affecting air-to-air visibility. The last section deals with the conclusions the author has reached in his investigations. There is much of interest for the general ophthalmologist as well as for the flight surgeon. In addition to investigating applied physiology, the author has uncovered a number of facts of basic physiological interest in respect to the function of the retina. This book will be of particular interest to flight surgeons, but, in addition, there is much of practical value for the general ophthalmologist.

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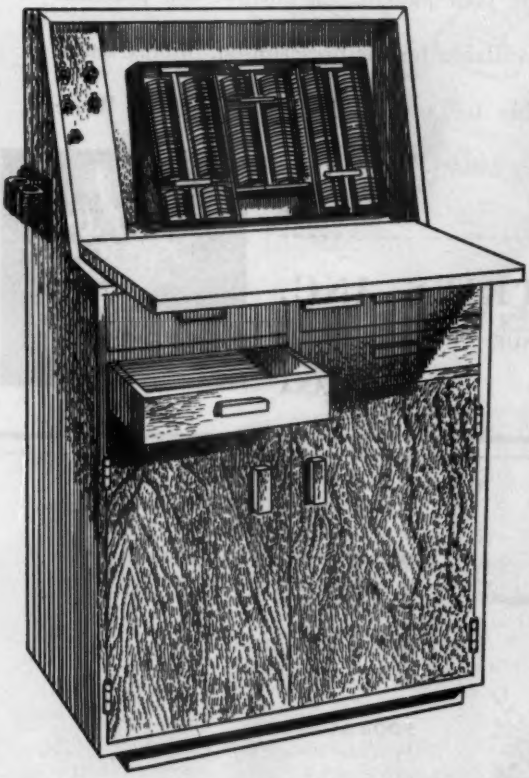

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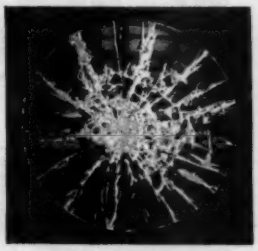

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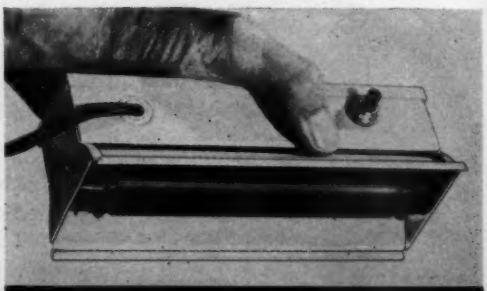

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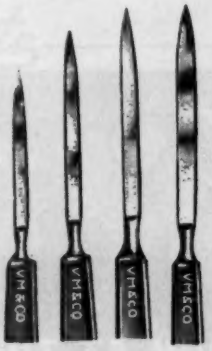

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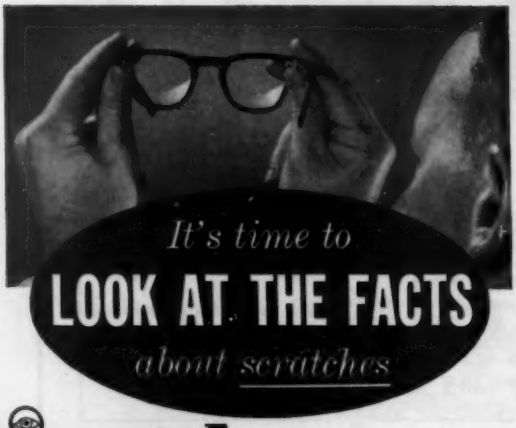

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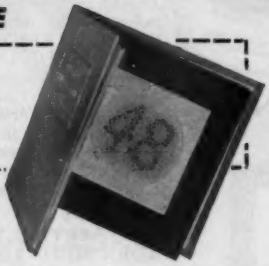

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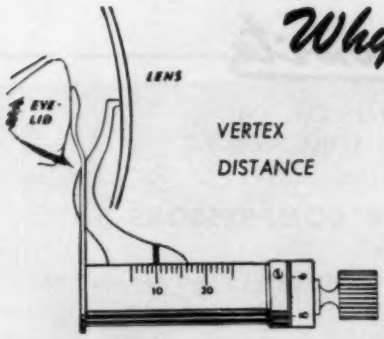

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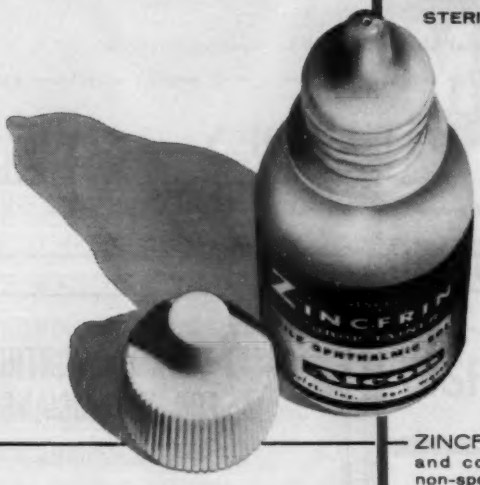

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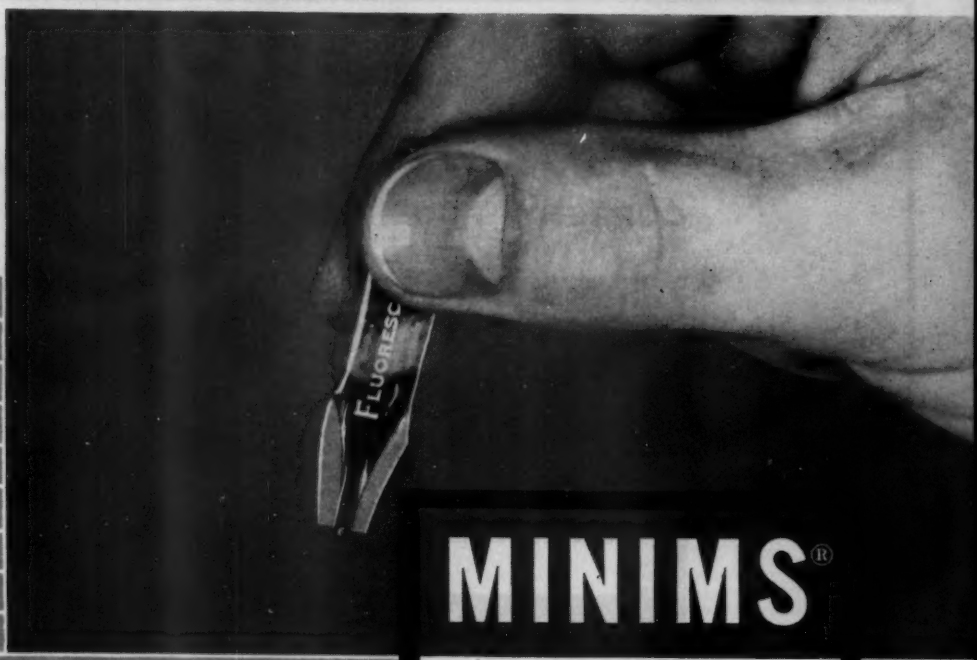

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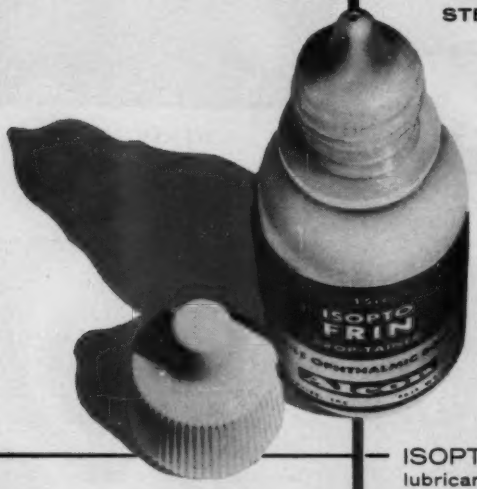

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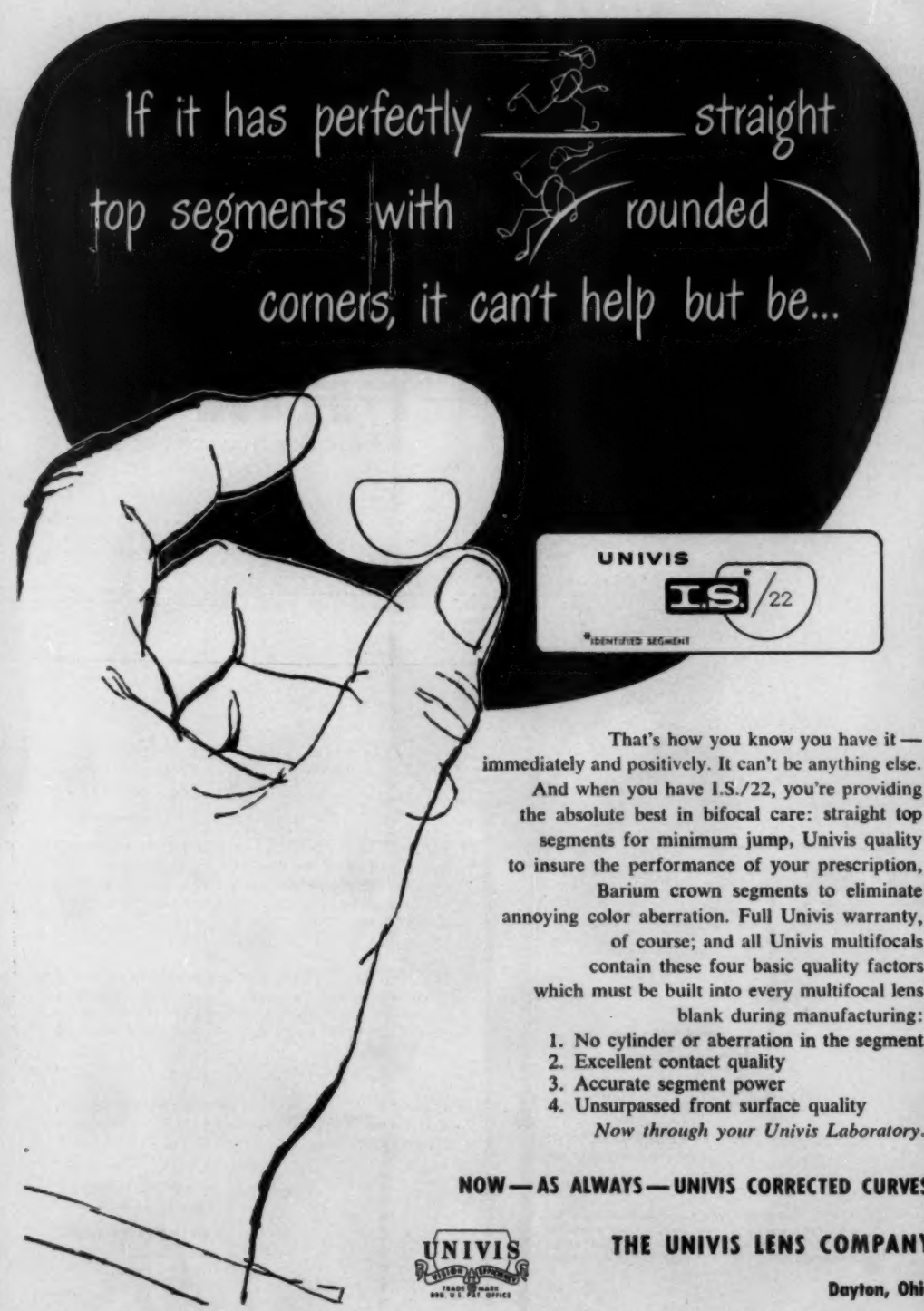

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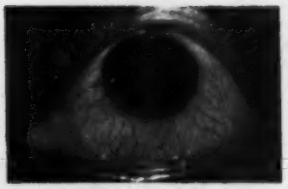

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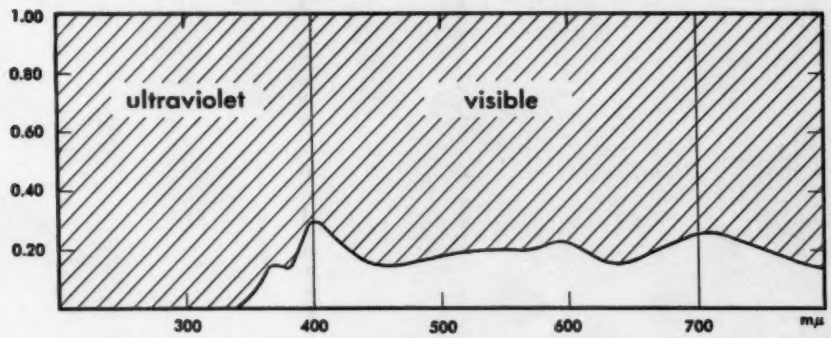

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